UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation **This Document Related To: All Cases**	**22md3043 (DLC)**

MEMORANDUM IN OPPOSITION TO DEFENDANTS' RULE 702 MOTION TO EXCLUDE DR. ANDREA BACCARELLI

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PRELIMINARY STATEMENT[1]

The *Daubert* inquiry "must focus on the [expert's] principles and methodologies." *Amorgianos v. Nat'l R.R. Passenger Corp*., 303 F.3d 256, 266 (2d Cir. 2002); *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 595 (1993) ("The focus, of course, must be solely on principles and methodology, not on the conclusions they generate."). Defendants do not lay a glove on Dr. Baccarelli's principles or methods. Instead, Defendants' motions boil down to a factual assertion: our interpretation of the studies is right; Dr. Baccarelli (and the study authors themselves) are wrong.

Defendants are entitled to that view. But they cannot ask this Court to embrace it as a matter of law, excluding the well-reasoned opinion of a preeminent public-health expert. Dr. Baccarelli deployed both the standard Bradford Hill methodology found in every epidemiology textbook plus the Navigation Guide methodology that provides a systematic and transparent way to document and evaluate causation. He has more than "good grounds" for his conclusions. *Amorgianos*, 303 F.3d at 267 (cleaned up). Any dispute on that score is for a factfinder, not a gatekeeper.

[redacted]

[redacted] Dr. Pinto-Martin admitted that scientists like Dr. Baccarelli, who have opined that there is a causal link between APAP, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), are employing "scientifically reasonable means to address the question using

[1] Defendants largely assert the same arguments across Plaintiffs' experts in three omnibus briefs, failing to assert proper Rule 702 challenges against each specific expert's testimony. Plaintiffs therefore incorporate by reference arguments made in their Oppositions to the Motions to Exclude Drs. Pearson, Hollander, Cabrera, and Louie.

the data that they have available." Ex. 25, Pinto-Martin Dep. Tr. at 504:11–14. She describes an "ongoing debate" among good-faith epidemiologists "about whether there is any causal association" here. *Id.* at 138:16–20. Dr. Faraone previously identified APAP as one of the "modifiable environmental risk factors for ADHD," which are "[c]auses of ADHD." Ex. 196, Faraone Dep. Ex. 771 at 2–3. Dr. Kolevzon co-authored a book chapter stating that, "among the potential risk factors" for autism, "prenatal use of acetaminophen is one possibility." Ex. 28, Kolevzon Dep. Tr. at 50:8–17. Though he now disavows his own publication, he at least concedes that the authors of the Bauer (2021) consensus statement are "good scientist[s]" who "have a real commitment to trying to understand environmental causes of autism." *Id.* at 71:22–73:1, 75:16–17.

Defendants' witnesses are right. Dr. Baccarelli is a "good," indeed an excellent, scientist who is on one side (the right side) of an "ongoing debate" among epidemiologists. Where that is so, Rule 702 entrusts juries to decide which side is right. *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 153 (1999) (If an expert's testimony lies within "the range where experts might reasonably differ," the jury, and not the trial court, should "decide among the conflicting views of different experts."); *see also Milward v. Acuity Specialty Prods. Grp., Inc*., 639 F.3d 11, 22 (1st Cir. 2011) (A *Daubert* court is not allowed to "t[ake] sides on questions that are currently the focus of extensive scientific research and debate.").

If there were any further doubt that Dr. Baccarelli's opinion lies within the range where experts might reasonably differ, the outside-of-litigation statements made by many authors of the published literature dispel it. These independent scientists analyzed the same question Dr. Baccarelli did—often based on a less-thorough literature review than he did—and they came to similar conclusions that causation is most likely. Ex. 1, Baccarelli Rep. at 7; *see infra* 17–19. Dr.

Baccarelli cannot be excluded for offering the same opinion that his scientific peers are offering in the peer-reviewed literature. *See In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 186 (S.D.N.Y. 2009).

The best Defendants can muster is that we cannot be 100% *certain* that APAP causes ASD and ADHD. Plaintiffs and Dr. Baccarelli have the humility to agree. Nothing in life or science is certain. But in law, what is quite clear is the applicable standard of proof: "preponderance of the evidence." *In re Ephedra Prods. Liab. Litig.*, No. 04 MD 1598 (JSR), 2005 WL 8178810 at *6 (S.D.N.Y. Sept. 20, 2005). Defendants prefer otherwise, claiming: "Where a study's results *could be explained* by confounding or bias that cannot be ruled out, that result *cannot* form the basis of a reliable causation opinion." Defs. ADHD Br. at 19–20, Dkt. 1162 (emphasis added). But that is not the law. *See Amorgianos*, 303 F.3d at 266 (holding that an expert need not "back his or her opinion with published studies that unequivocally support his or her conclusions"); *In re Ephedra Prod. Liab. Litig*, 393 F. Supp. 2d 181, 188 (S.D.N.Y. 2005) (same); *In re Bair Hugger Forced Air Warming Devices Prods. Liab. Litig.*, 9 F.4th 768, 779 (8th Cir. 2021) (same); *United States v. W.R Grace*, 504 F.3d 745, 765 (9th Cir. 2007) (same). Nor is it the way that epidemiology works. There are hundreds of associations that have been deemed causal based on evidence that could not *definitively* rule out alternative explanations—the link between valproic acid, ASD, and ADHD; the link between second-hand smoke and cancer; even the initial link between active cigarette smoking and lung cancer, to name just a few. Thankfully, actual scientists do not share Defendants' blinkered view of when a causal inference can be made.

Throughout their briefs, Defendants point to FDA's statements that the agency was unable to make a definitive "determination of causality" here. Defs. ADHD Br. at 1; Defs. ASD Br. at 1, Dkt. 1160. But as explained in greater detail below, the FDA record in fact confirms that *Plaintiffs*

are correct on the question before the Court: reasonable scientists can and do disagree on the question of causation. In any event, FDA's views do not control the *Daubert* inquiry, as the United States concedes. Dkt. 1105 at 1–2. That is why at least one district court has been reversed for accepting Defendants' repeated argument that FDA statements are determinative. *See Bair Hugger*, 9 F. 4th at 789 (reversing grant of Rule 702 motion where the district court relied on the fact that FDA said it had been "unable to identify" even "a consistently reported *association*" in the literature) (emphasis added).

Dr. Baccarelli transparently applied time-tested methods to a large body of evidence to conclude that the link between APAP and ASD/ADHD is more likely than not causal. Reasonable scientists could and have reached that same conclusion. Reasonable jurors could believe them. Defendants' motion to exclude Dr. Baccarelli must be denied.

BACKGROUND

I. Dr. Baccarelli's Credentials

Dr. Andrea Baccarelli is one of the most highly-qualified and widely-respected scientists in his field. He is Chair of the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health, one of the top four schools of public health in the country. Dr. Baccarelli runs the school's Laboratory of Precision Environmental Health where he and his team "investigate links between environmental exposures and health outcomes." He also directs the "NIEHS P30 Center for Environmental Health and Justice," which "investigat[es] the effects of toxic chemicals." Ex. 1, Baccarelli Rep. at 9, 11.

Before joining the Columbia faculty, he was Associate Professor of Environmental Epigenetics at the Harvard School of Public Health. He holds a Ph.D. in Toxicology and Occupational Health (*summa cum laude*) from the University of Milan. He holds an M.S. in

Epidemiology (again *summa cum laude*) from the University of Turin. And he is a physician, holding an M.D. from the University of Perugia (once again, *summa cum laude*). *Id.* at 9.

Dr. Baccarelli has published more than *600* peer-reviewed papers, including 249 in the past five years alone. *Id.* at 10. Several of those papers concerned "the effects of environmental toxins, including acetaminophen, on neurodevelopment." *Id.* Before being retained for this litigation, he "led a large human study funded by the National Institutes of Health that investigated the impact of prenatal acetaminophen use during pregnancy on children's neurodevelopment." *Id.* Dr. Baccarelli is an inquisitive scientist who follows the evidence wherever it leads him. When he began looking into the link between APAP, ASD, and ADHD, he was "a nonbeliever," Ex. 20, Baccarelli Dep. Tr. at 283:1–6, "absolutely . . . convinced" that APAP was "*not* associated with adverse neurodevelopmental outcomes." *Id.* at 19:7–12 (emphasis added). Indeed, he co-authored a study—Laue (2019)—which showed no association between APAP and a child's IQ.[2]

But in the years since the Laue study, the evidence has continued to pile up. In 2020, he co-authored the Baker study that found "that acetaminophen exposure detected in meconium was associated with increased risk of ADHD, with a dose-response association detected." Ex. 1, Baccarelli Rep. at 10–11.[3] There have been many others like it. *See, e.g.*, Ex. 37, Alemany (2021); Ex. 83, Liew (2019); Ex. 46, Ji (2020); Ex. 33, Ricci (2023). As Dr. Baccarelli testified, since the Laue publication, there "have been five years' worth of data that are damning. I mean really." Ex.

[2]Defendants are wrong that Laue (2019) "directly contradict[s]" Dr. Baccarelli's opinions. Defs. ASD Br. at 69. It had a sample size of just 118 and did *not* evaluate ASD or ADHD. It was instead a study of children's *intelligence*. Ex. 1, Baccarelli Rep. at 108. As Dr. Baccarelli and his co-authors made clear, "behavior and intelligence are different neuropsychological constructs," meaning that the Laue 2019 results "cannot be directly compared with other studies" on ASD or ADHD. Ex. 173, Laue (2019) at 141–42; *see also* Ex. 20, Baccarelli Dep. Tr. at 266:22–267:1 ("[K]ids with ADHD, they don't have lower intelligence usually. And children with ASD might even have higher [intelligence].").

[3] Defendants argue that Baker (2020) "directly contradict[s]" his opinions. Defs. ASD Br. at 69. But the Baker authors stated that their results "add evidence in support of the association between prenatal acetaminophen use and child ADHD" and that institutions should "reevaluat[e] the evidence regarding the safety of fetal acetaminophen exposure." Ex. 71, Baker (2020) at 1080. That kind of result cannot "directly contradict" a causation opinion.

20, Baccarelli Dep. Tr. at 269:23–270:3. Before he became an expert in this litigation, Dr. Baccarelli saw the mounting evidence and "started to believe . . . there was a problem." *Id.* at 45:18–22; *see also id.* at 47:1–5 ("Before starting to work on this case, I became pretty convinced, or almost entirely convinced, reasonably convinced, that there was a causal association.").[4] And when he reviewed the literature in detail, he was "blown away by the consistency," a "level of consistency I've never seen before in my life." *Id.* at 45:23–46:6.[5]

Dr. Baccarelli's scholarship is influential and high impact. His papers have been cited a staggering "47,300 times in the scientific literature," Ex. 1, Baccarelli Rep. at. 10. He is one of the most cited and influential academics in the world in *any* field, epidemiology or otherwise: In 2020—and every year since—the Web of Science organization (based on their citations database) has included him on its short list of "Highly Cited, World's Most Influential Researchers" of the past decade. *Id.*

For his groundbreaking work on how the environment affects the human epigenome, Dr. Baccarelli was elected to the National Academy of Medicine. *Id*. at 9, 11. Election to the Academy is among the most selective appointments in all of science, with members voted in based on their distinguished and continuing achievements in their relevant field.[6]

[4] Defendants suggest that Dr. Baccarelli's "about face" is due to him "being paid by plaintiffs," but that suggestion is as incoherent as it is offensive. Defs. ASD Br. at 71. They are suggesting that a world-famous academic decided to take a position he knew was wrong, and along the way admit falsely that he had been wrong before. That is fantastical. It is also contrary to the timeline, since he changed his view "*[b]efore* starting to work on this case."

[5] Defendants say that the mounting literature "is not a credible explanation," but the facts speak for themselves: Dr. Baccarelli initially did not believe there was anything to see here when he had not read the literature; then he read it and realized there was a serious problem. That represents exactly the "level of intellectual rigor" that good epidemiologists employ. *Kumho Tire*, 526 U.S. at 152.

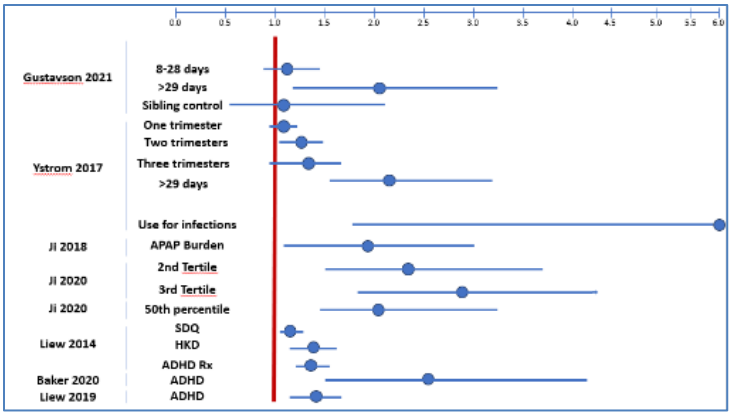
[6] Defendants' expert Dr. Pinto-Martin, who is not an elected member of the National Academy of Medicine, conceded that "it's pretty hard to get elected," and that it's an "extremely impressive credential," a "hard appointment to get." Ex. 25, Pinto-Martin Dep. Tr. at 43:9–18.

II. Dr. Baccarelli Considered an Extensive Body of Evidence to Reach His Conclusions.

"Epidemiologic studies are the primary generally accepted methodology for demonstrating a causal association between a chemical compound and a . . . disease." Ex. 35, Ref. Manual at 553 n.11 (quoting *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 800 (N.D. Ohio 2004)). When "accompanied by a reliable expert opinion that the association is causal," even a *single* "epidemiological study identifying a statistically significant association between the use of a drug and a particular adverse effect" "is 'powerful' evidence of general causation." *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1307 (N.D. Fla. 2018) (quoting *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1198 (11th Cir. 2002)). Here there are more than a dozen studies, involving hundreds of thousands of women and children from around the world. Ex. 1, Baccarelli Rep. at 79–97 (describing literature for ADHD); *id.* at 97–104 (describing literature for ASD). That is why Dr. Baccarelli—who has created and evaluated epidemiological literature full-time for the past twenty years—testified that the literature is among the most compelling he has ever seen. Ex. 20, Baccarelli Dep. Tr. at 46:1–6.

A. Studies Showing a Link Between Prenatal APAP Exposure and ADHD

As Dr. Pinto-Martin admitted, there are (even by her count) *13* statistically significant results showing a link between prenatal APAP exposure and ADHD diagnosis. Ex. 25, Pinto-Martin Dep. Tr. at 170:25–171:4. The forest plot is striking. Ex. 36, Pinto-Martin Dep. Ex. 633; Ex. 25, Pinto-Martin Dep. Tr. at 261:18–262:5.



Every single one of the 17 results is positive—*i.e.*, in 100% of the long-term use studies that Dr. Pinto-Martin identified, the women who took APAP had children with ADHD at higher rates than the women who did not. Ex. 25, Pinto-Martin Dep. Tr. at 167:15–23 (agreeing that "100 percent of these studies had a point estimate showing a positive association between prenatal APAP exposure and the risk of ADHD diagnosis"). And the number of statistically significant results increases further when meta-analyses and studies with endpoints other than ADHD diagnoses are added to the analysis. Ex. 1, Baccarelli Rep. at 92–97 (describing the results of the Masarwa, Gou, Alemany, and Ricci meta-analyses, all of which produced statistically significant results). In the Alemany meta-analysis, there was a "consistent pattern of results" observed "for the association between prenatal APAP exposure and ADHD symptoms," with a sample of "70,000 children" demonstrating that "children prenatally exposed to acetaminophen were" "21% more likely to have ADHD symptoms." Ex. 37, Alemany (2021) at 999–1000. Even FDA, although not yet willing to draw a causal inference, agrees that the association between prenatal APAP exposure and ADHD has been consistently demonstrated. *See* Dkt. 483-1 at FDACDER0000114 ("[The] studies examined in this review along with the reviewed meta-analyses suggest a consistent association between APAP or long durations of prenatal APAP exposure and ADHD."). Perhaps for this reason, Defendants do not even contest that a clear

association with ADHD exists. *Compare* Defs. ASD Br. at 27 (arguing that there is no "'clear-cut' association between prenatal acetaminophen exposure and ASD") *with* Defs. ADHD Br. (making no argument on association between APAP and ADHD).

B. Studies Showing a Link Between Prenatal APAP Exposure and ASD

For ASD, the literature is more limited—in part because the condition itself is rarer—but the forest-plot results are equally compelling. *See* Ex. 38, Pinto-Martin Dep. Ex. 634. As Dr. Pinto-Martin admits, even by her count, all but one of the results (one subgroup in one study) show that "the woman who was exposed to APAP . . . had a higher rate of having a child with ASD." Ex. 25, Pinto-Martin Dep. Tr. at 262:23–263:22. Many of the results are statistically significant—including results from Liew (2016a), an enormous study that Dr. Pinto-Martin agreed was the highest quality in the literature. *Id.* at 21:9–16. There were also two meta-analyses that both reported statistically significant results. Ex. 37, Alemany (2021); Ex. 65, Masarwa (2018). As the authors of the Alemany meta-analysis put it, "[t]he association between prenatal acetaminophen exposure use and [autism] symptoms was consistently positive." Ex. 37, Alemany (2021) at 1000.[7]

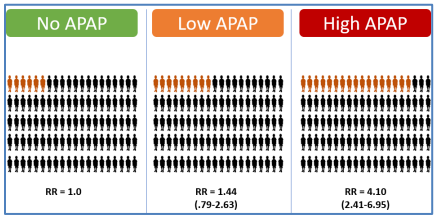
C. Studies Showing a Dose Response

"A dose-response relationship means that the greater the exposure, the greater the risk." Ex. 35, Ref. Manual at 603. When a dose-response *is* present, it is "strong" "evidence that the relationship between an agent and disease is causal." *Id*. The literature demonstrates a clear dose response, *i.e.*, the more APAP a woman takes while pregnant, the higher her risk of having a child with ASD or ADHD. Six studies have investigated whether there is a dose-response relationship

[7] The number of statistically significant results increases further when considering studies that looked at symptoms of ASD rather than ASD diagnoses alone. For example, the Avella-Garcia study found that male children exposed to APAP while in utero "presented [with] more autism symptoms" than unexposed children—symptoms measured using the Childhood Autism Spectrum Test. Ex. 39, Avella-Garcia (2016) at 1992. There are many others like it. Ex. 1, Baccarelli Rep. at 158–73, App. 1 at 14–21.

between prenatal APAP exposure and ADHD. Two focused on ASD. *All eight* showed a dose response. *See generally* Ex. 1, Baccarelli Rep. at 163–64, App. 1. As the Alemany authors put it, "previous studies have shown dose-response effects for both [autism] and ADHD symptoms." Ex. 37, Alemany (2021) at 1000.

Although a dose-response relationship was demonstrated even in studies relying on maternal self-reports of exposure, the relationship is particularly striking in studies that were able to measure APAP levels directly. The results of the Baker (2020) study are displayed below. *See* Ex. 40, Pinto-Martin Dep. Ex. 637.



As the level of APAP in the child's meconium increases, so does the risk of being diagnosed with ADHD years later. For children with high levels of APAP in their meconium, the risk ratio was 4.10, corresponding to an increased ADHD risk of 310%.

The results from Ji (2020) are similar. *See* Ex. 41, Pinto-Martin Dep. Ex. 638 at 2. Children with the highest levels of APAP in their umbilical-cord blood were 262% more likely than those in the lowest tertile to be diagnosed with autism years later—nearly a *quadrupling* of the autism risk. Ex. 46, Ji (2020) at 188. The dose-response results for ADHD were similar. *See* Ex. 41, Pinto-Martin Dep. Ex. 638 at 1. Children in the second tertile of APAP levels showed a more-than-doubling of risk and children in the top tertile showed a near-tripling of the risk.

D. Evidence Against Confounding

In response to this robust body of evidence, Defendants primarily argue that these dozens of results must be the result of confounding—specifically confounding by indication or

confounding by genetics. That is certainly a theoretical *possibility*, though not a likely one based on the available evidence. Ex. 35, Ref. Manual at 553 ("It is important to emphasize that all studies have 'flaws' in the sense of limitations."); *id.* at 583 ("Most epidemiologic studies have some degree of bias that may affect the outcome."). No matter how well-designed a study is, "there is *always* a risk that an undiscovered or unrecognized confounding factor may contribute to a study's findings." *Id.* at 593 (emphasis added). But the Reference Manual instructs courts to "keep that risk in perspective." *Id.* "Often the mere possibility of uncontrolled confounding is used to call into question the results of a study. This was certainly the strategy of some seeking, or unwittingly helping, to undermine the implications of the studies persuasively linking cigarette smoking to lung cancer." *Id*. That quote was prescient. The type of confounding that Defendants appeal to here—confounding by genetics—is *identical* to what skeptics of the cigarette/lung-cancer link pointed to. Defendants' expert Dr. Pinto-Martin admitted that a notable smoking skeptic's "illustration of the potential role of genetic confounding [in the cigarette/lung-cancer literature] is similar to what I'm arguing." Ex. 25, Pinto-Martin Dep. Tr. at 281:10–12.

1. Numerous Study Authors Have Stated That Confounding Likely Does Not Explain the Link Between Prenatal APAP Exposure, ASD, and ADHD.

Aware that confounding is always possible, epidemiologists attempt to control for it. The scientists working in this literature have employed numerous methods to find evidence of confounding rather than causation. Those efforts have generally failed. "[C]onfounding alone is an unlikely explanation for the associations reported in these studies," Ex. 77, Bornehag (2017) at 101; it is "unlikely that the observed relationship between prenatal acetaminophen and [autism spectrum conditions] and ADHD symptoms is entirely explained by unmeasured confounding," Ex. 37, Alemany (2021) at 1001; various study designs have provided "additional evidence against confounding," Ex. 42, Olsen & Liew (2017) at 1395; "several lines of reasoning suggest that bias,

confounding, and chance are not solely responsible," Ex. 43, Bauer & Kriebel (2018) at 134.[8] That is a powerful indication that Dr. Baccarelli's methodology (and opinion) are reasonable.

2. Most Confounders Have Been Controlled for in This Robust Literature.

Why do these independent scientists agree that confounding is unlikely? It is not simply because so many studies "all find statistically significant results," but also "[m]ore important[ly]" because of "the methods and bias anal[yses] that have been applied trying [unsuccessfully] to make the association 'go away.'" Ex. 42, Olsen & Liew (2017) at 1396. To begin with, the studies control (directly) for a wide range of potential confounders. *See* Ex. 35, Ref. Manual at 596 ("If researchers have good data on potential confounders, they can control for those confounders in the data analysis" using "stratification or multivariate analysis."). Maternal age, birth weight, maternal smoking, maternal alcohol use, maternal BMI, maternal psychiatric history, maternal fever, parental education levels and socioeconomic status, use of other medications, gestational age, family history and many more—all of these have been *explicitly* controlled for. *See, e.g.*, Ex. 44, Liew (2014) at 318; Ex. 45, Liew (2016a) at 955; Ex. 46, Ji (2020) at 186; Ex. 37, Alemany (2021) at 999. The results remained robust. Even when (mathematically) comparing two children born to families with similar smoking history, socioeconomic status, psychiatric histories, and so on, the child exposed to APAP still had a higher risk of ASD and ADHD.

3. The Negative-Control Analyses Suggest That Confounding Is Unlikely.

The attempts to address confounding did not end there. After controlling for measurable confounders, researchers also tried to determine whether *unmeasured* confounders—in particular

[8] As the Federal Reference Manual makes clear, and as Defendants' own experts admit, when there is an observed association between an exposure and a disease, there are only four theoretical possibilities: chance, bias, confounding, and causation. Ex. 35, Ref. Manual at 572; Ex. 25, Pinto-Martin Dep. Tr. at 68:10–19 (conceding that there are no "other theoretical possibilities"). So when the Bauer and Kriebel (2018) authors exclude "bias, confounding, and chance," they are suggesting that causation is the most likely explanation. Ex. 43, Bauer & Kriebel (2018) at 134. It is the only explanation left.

genetics—might be driving the results. For example, to address the possibility that women who are genetically predisposed to have children with ADHD and ASD might (somehow) also be genetically predisposed to take APAP, researchers conducted a series of "negative controls." They looked at whether a mother's use of APAP *before* or *after* pregnancy was associated with neurodevelopmental disorders (NDDs). After all, if women who genetically are more likely to have children with ASD and ADHD are somehow more likely to consume APAP, the researchers reasoned, then they should be more likely to take more APAP before and after pregnancy as well.

That is not what the negative-control studies showed. Instead, the Ystrom study showed *no* association between a mother's use of APAP *before* pregnancy and her child's risk of ADHD. Ex. 85, Ystrom (2017) at 6 ("Maternal preconceptional use was not associated with ADHD . . . [This] is consistent with a causal link."). The Liew (2019) study showed *no* association between a mother's use of APAP *before* or *after* pregnancy and her child's risk of ADHD. Ex. 83, Liew (2019) at 771 ("[T]he absences of associations with acetaminophen use in the prepregnancy and postpregnancy periods . . . suggest that variables that do not vary over a few years—such as genetics, maternal chronic diseases or socioeconomic status—do not explain the association observed for acetaminophen exposure at the time of pregnancy."). And the Stergiakouli study showed *no* association between a mother's use of APAP *after* pregnancy and her child's risk of hyperactivity, emotional, and conduct problems. Ex. 50, Stergiakouli (2016) at 967 ("[m]aternal postnatal acetaminophen use" was "not associated" with the relevant NDDs).

That is powerful evidence that genetic confounding is not the culprit. Once again, Dr. Baccarelli's opinion is in accord with the study authors. The Liew authors suggest that "genetics" "do not explain the association." Ex. 83, Liew (2019) at 771. The Stergiakouli study authors assert that the associations "are consistent with an intrauterine mechanism," *i.e.*, a causal link. Ex.

50, Stergiakouli (2016) at 967. And the Ystrom study authors state that their negative control analysis is "consistent with a causal link."[9] Ex. 85, Ystrom (2017) at 6.

4. Defendants' Own Experts Admit That the Evidence Does Not Strongly Suggest that Confounding Explains the Repeatedly Observed Association.

Defendants' lawyers argue there is a scientific consensus that confounding explains these results. Their own experts do not toe that party line. Dr. Pinto-Martin agrees that in order for "genetics" to confound the association, "genetics" would need to *both* cause autism *and* be associated with a woman's propensity to take APAP *while pregnant*. *See* Ex. 48, Pinto Martin Dep. Ex. 632; Ex. 25, Pinto-Martin Dep. Tr. at 220:22–25. Yet she agrees that "we don't have sufficient evidence to really support that [genetics] as a [] confounding variable" for autism. Ex. 25, Pinto-Martin Dep. Tr. at 153:19–21. That was no slip of the tongue. The Leppert study looked specifically at whether the maternal genes associated with a child's autism are also associated with APAP use during pregnancy. Ex. 82, Leppert (2019). The answer was "no." *See* Ex. 25, Pinto-Martin Dep. Tr. at 157:23–158:8 (conceding that the Leppert study reported a "null" association).[10]

For ADHD, the Stergiakouli study did the same thing, looking at whether the genes associated with ADHD were related to a mother's use of APAP. Again the answer was "no": the "index of ADHD genetic risk in the mothers was not associated with acetaminophen use during pregnancy," which suggested that "unmeasured familial factors"—*i.e.*, genetics—do *not* explain the associations. Ex. 50, Stergiakouli (2016) at 967. Indeed, the Stergiakouli authors stated that this result was consistent *not* with genetic confounding, but rather "an intrauterine effect," *i.e.*,

[9] Dr. Faraone agreed that "if you've got a valid negative control, that can control for confounding." Ex. 31, Faraone Dep. Tr. at 238:23–239:6.

[10] Defense expert Dr. Faraone gave a similar admission, conceding that he had "no data" showing that women with ADHD take more APAP while pregnant than they do when not pregnant—he made clear that this was "just an opinion" of his. Ex. 31, Faraone Dep. Tr. at 262:23–263:8. And in a book chapter that Dr. Kolevzon co-authored, he stated that the studies had "adjusted for confounding variables" but the results remained "considerably robust and statistically significant." Ex. 98, Kolevzon Dep. Ex. 494 at 198.

causation. *Id*. And although the Leppert study found some evidence of a link between ADHD genetics and APAP use, Dr. Pinto-Martin admitted that the results there were "barely" statistically significant and "not incredibly powerful." Ex. 25, Pinto-Martin Dep. Tr. at 161:8–17. It is easy to cry confounding, because any conscientious epidemiologist will concede it is always *theoretically* possible—as Dr. Baccarelli did here. It is particularly easy to cry "confounding by genetics," given how difficult "genetics" are to measure. But there is no compelling *evidence* that genetic confounding explains the repeatedly observed associations.

Defendants' other alibi for this association is confounding by indication. They hypothesize that perhaps ASD and ADHD are being caused by the fever, infection, and so on for which the mother is taking APAP in the first place. But the possibility of confounding by indication has been studied extensively and rejected by the authors publishing in this literature, as Dr. Pinto-Martin conceded. *Id.* at 319:16–17.[11] Study authors have employed stratified analyses to look *only* at women who took APAP long-term for certain indications. *See* Ex. 85, Ystrom (2017) at 6 (showing a statistically significant risk for women who took APAP for "fever and infections," for "pain conditions" and for "indication not specified"). Other authors have controlled for indication directly in their analyses. *See* Ex. 37, Alemany (2021) at 1000–01 ("[P]otential indications for acetaminophen use were included as covariates."); Ex. 43, Bauer & Kriebel (2018) at 134 ("Reported associations between prenatal APAP exposure and health outcomes in children remained in all nine studies after adjustments for indication for use."). The results largely have been the same: no evidence that confounding by indication explains the association. *See* Ex. 33, Ricci (2023) at 2 ("Confounding by indication did not explain the association."); Ex. 77, Bornehag

[11] Dr. Pinto-Martin also testified that she is not sure that fever causes autism *at all*, Ex. 25, Pinto-Martin Dep. Tr. at 125:14–15 (hypothesizing that "fever itself is not the causal agent"), which means it cannot confound *anything* in the autism literature. Ex. 35, Ref. Manual at 574 (a confounder must be a "true causal factor").

(2018) at 101 ("[O]ur available data do not support confounding by indication."); Ex. 42, Olsen & Liew (2017) at 1395 ("[I]t is too simple and not justified to explain away the possibility of causality by mentioning confounding, especially confounding by indication."). [redacted]

5. The Sibling Control Studies Do Not Prove Confounding.

Faced with this compelling evidence, Defendants hang their hat on a single subset of studies in this literature: so-called sibling-control studies that examine whether a sibling exposed to APAP in utero has a greater risk of developing an adverse outcome than her unexposed sibling. As Dr. Pinto-Martin admitted, however, a study showing a greater risk via a sibling-control design is "evidence against genetic confounding." Ex. 25, Pinto-Martin Dep. Tr. at 406:14–15. And the Brandlistuen study showed exactly that—*i.e.*, the sibling exposed to APAP while in utero had poorer gross motor development, communication skills, externalizing and internalizing behavior, and hyperactivity levels. Ex. 51, Brandlistuen (2013) at 1702. These traits are signature symptoms of both ADHD and ASD, providing compelling evidence that genetic confounding cannot explain this literature.

So Defendants are forced to argue that only *one* sibling study, Gustavson (2021), should count. But a reasonable scientist could disagree with this convenient myopia. To begin with, the sibling exposed to APAP in the Gustavson study still had a 6% higher chance (RR = 1.06) of being diagnosed with ADHD than the sibling who was not exposed. Ex. 52, Gustavson (2021) at 7. Although that result was quite small in magnitude—close to null—and not statistically

significant,[12] that is no surprise given the size of the study. Most of the studies in this literature had sample sizes in the tens of thousands. *See, e.g.*, Ex. 45, Liew (2016a) at 951 (64,322 sample size); Ex. 44, Liew (2014) at 313 (64,322 sample size); Ex. 37, Alemany (2021) at 993 (73,881 mother-child pairs sample size). Gustavson had an operative sample size of ***34***. Ex. 52, Gustavson (2021) at 5.

That kind of study is extraordinarily underpowered. Ex. 25, Pinto-Martin Dep. Tr. at 453:10 ("I agree the sample size is small."). Hence the most likely explanation for the non-significant finding in the Gustavson sibling control is its tiny sample size. As the Federal Reference Manual makes clear, "[w]hen a study with low power fails to show a significant effect, the results may . . . be more fairly described as inconclusive than negative." Ex. 35, Ref. Manual at 254. That is why the Gustavson study authors *themselves* noted that "statistical power to detect within effects was relatively low. Hence, these results should be interpreted with caution." Ex. 80, Gustavson Supp. Information, App. S2 § 2.3. As Dr. Pinto-Martin conceded, "Does [Gustavson] prove that this is all about genetics? No." Ex. 25, Pinto-Martin Dep. Tr. at 466:15–16.

E. Independent Scientists Have Suggested That Causation Is Most Likely.

Dr. Baccarelli has a good deal of company in the scientific community. That is all the more notable given the conservatism of his field. Ex. 35, Ref. Manual at 599 ("[R]esearchers are conservative when it comes to assessing causal relationships, often calling for stronger evidence and more research before a conclusion of causation is drawn."). The authors of the Olsen and Liew paper considered "observational data from several cohorts" employing "different analytical

[12] As the Reference Manual notes, this kind of result is still evidence of an effect, albeit weaker evidence: "If the relative risk is greater than 1.0, the risk in exposed individuals is greater than the risk in unexposed individuals. There is a positive association between exposure to the agent and the disease, which could be causal." Ex. 35, Ref. Manual at 567; *id.* at 578 n.85 ("The cold statement that a given relationship is not 'statistically significant' cannot be read to mean there is no probability of a relationship.") (quoting *Allen v. United States*, 588 F. Supp. 247, 417 (D. Utah 1984)).

options" and concluded that "[t]hese research findings have increased the probability that the association is causal." Ex. 42, Olsen & Liew (2017) at 1395. The authors of the Gou meta-analysis noted that "the most recent seven studies" showed a significantly increased risk and that "[t]hese research findings lend weight to the hypothesis that the association is causal." Ex. 54, Gou (2019) at 204. The authors of the Stergiakouli study concluded that their findings were "consistent with an intrauterine effect," *i.e.*, with causation. Ex. 50, Stergiaklouli (2016) at 967. The Briggs Textbook says that although APAP was "originally thought not to cause embryo-fetal harm, this assessment must change because of recent data" regarding the risk of neurodevelopmental disorders. Ex. 172, Pinto-Martin Dep. Ex. 613.[13] The authors of the Alemany meta-analysis went so far as to conduct their *own* independent Bradford Hill analysis, concluding that five of the "causal criteria" were satisfied: consistency, temporality, dose-response, biological plausibility, and coherence. Ex. 37, Alemany (2021) at 1000.[14]

The lead author of that study—Sylvia Alemany—gave an interview in which she said: "what emerges from our results is that when [APAP] is being consumed when it is not strictly necessary, perhaps its consumption should be decreased and with it, the likelihood of developing certain neurodevelopmental problems in the future."[15] Two authors of the consensus statement, Dr. Swan and Dr. Bauer, have made similar statements. Dr. Swan stated "the fact that as time

[13] The Neurologic Health Foundation similarly counsels pregnant mothers that "acetaminophen has been linked to increased risk of having a child with ADHD" and "possibly linked to an increased risk of having a child with autism." James B. Adams et al., *Healthy Child Guide: Preconception & Pregnancy Recommendation for a Healthy Child*, Neurologic Health Foundation, 34 (Feb. 2016), https://health.ucdavis.edu/mindinstitute/resources/resources_pdf/hcg-feb-2016.pdf.

[14] These statements by independent scientists make this case very different from *Mirena* and *Daniels-Feasel*, which Defendants cite extensively. There, "[o]utside [the] litigation, there [was] a complete absence of scholarship opining that Mirena, or for that matter any [similar] contraceptive, is a cause of [the disease at issue]." *Mirena*, 341 F. Supp. 3d at 247; *see also Daniels-Feasel v. Forest Pharms., Inc.,* No. 17 CV 4188-LTS-JLC, 2021 WL 4037820 at *19 (S.D.N.Y. Sept. 3, 2021) (expert was unable to cite *any* "peer-reviewed study" suggesting causation). Not so here.

[15] *Sílvia Alemany (ISGlobal): "I think the use of paracetamol during pregnancy should be monitored more tightly"*, El·lipse (June 22, 2021), https://ellipse.prbb.org/silvia-alemany-isglobal-i-think-the-use-of-paracetamol-during-pregnancy-should-be-monitored-more-tightly.

progresses, we see stronger and stronger evidence suggests that we've only been underestimating risk."[16] Dr. Bauer, for her part, stated that "we should reduce our use of acetaminophen when possible throughout the entire pregnancy."[17]

These statements—in which independent scientists have (themselves) suggested that causation is at least a reasonable inference, and often suggested it is the most likely one—demonstrate conclusively that Dr. Baccarelli's methods and opinions lie within "the range where experts might reasonably differ." *Kumho Tire*, 526 U.S. at 153. When a question is "currently the focus of extensive scientific research and debate," a court simply may not "t[ake] sides." *Milward*, 639 F.3d at 22. Defendants' experts admit that there is an "ongoing debate about whether there is any causal association." Ex. 25, Pinto-Martin Dep. Tr. at 138:18–19. It follows *per force* that Dr. Baccarelli's testimony is admissible.

F. Even JJCI Recognizes That There Is Evidence of Causation.

Although Defendants' attorneys claim there is *no* evidence APAP can cause ASD or ADHD, [redacted]

[16] Isabella Cueto, *New Research Cautions About Possible Risks of Acetaminophen Use During Pregnancy*, STAT (Oct. 6, 2023, 1:31 p.m.), https://www.statnews.com/2021/09/23/new-research-cautions-about-possible-risks-of-acetaminophen-use-during-pregnancy/. Dr. Swan is, by Defendants' expert's own admission, a reasonable scientist. Ex. 28, Kolevzon Dep. Tr. at 75:8–17 (admitting Dr. Swan "is a good scientist."); Ex. 25, Pinto-Martin Dep. Tr. at 183:2–5 (Dr. Pinto-Martin—who was one of Dr. Swan's students—describing Swan as "a solid biostatistician.").

[17] Cueto, *supra* note 16.

III. Legal and Regulatory Background.

The evidence with respect to APAP, ASD, and ADHD is compelling. Indeed, the evidence here is *stronger* than the evidence justifying warnings mandated for valproic acid and stronger than the evidence deemed sufficient to satisfy *Daubert* in past Second Circuit cases. And while Defendants repeatedly invoke FDA's statements as a reason to exclude Dr. Baccarelli, those statements are not relevant to the *Daubert* inquiry at all. In any event, the FDA record confirms that reasonable experts can view the evidence in the same way that Dr. Baccarelli does.

A. The Valproic Acid Label Demonstrates That Causal Inferences Can Be Made on the Basis of Evidence Less Robust Than the Evidence Here.

As Dr. Baccarelli notes, the FDA-approved label for valproic acid—a drug used to treat seizures and bipolar episodes—states that "the weight of the evidence supports a causal association" between in-utero exposure to that drug, ASD, and ADHD. Ex. 1, Baccarelli Rep. at 53, 167; Ex. 56, VPA Label at §§ 5.3, 5.4. That causal determination was made based on weaker epidemiology than is present here. In support of causation, the valproic acid label cites just two observational studies. *Id.*; Ex. 58, Christensen (2013); Ex. 59, Christensen (2019). As with the APAP literature, those studies noted the theoretical possibility of genetic confounding and confounding by indication. Ex. 58, Christensen (2013) at 7 ("This suggests confounding effects of maternal epilepsy or interaction between genetic susceptibility and valproate."); Ex. 59, Christensen (2019) at 9. ("We cannot rule out that the observed risk increase for ADHD is at least partially explained by the mother's health condition."). And neither of them made a definitive conclusion about causation. *Id.* at 10 ("Replication of our findings . . . is warranted."); Ex. 58, Christensen (2013) at 2 (concluding only that an "associat[ion]" was found).[18] Indeed, Defendants

[18] The data used to make the causal inference for ADHD was particularly equivocal. All risk ratios were well below 2.0. Ex. 59, Christensen (2019) at 5–6. There was a full "meta-analysis of 4 studies" that "did not find an association

(wrongly) claim to this day that "scientists have not concluded that the [valproic acid] association is causal." Defs. ASD Br. at 7. Nevertheless, outside of litigation, the makers of valproic acid, the FDA employees who approved the label, and indeed Defendants' own experts all agree that causation is the most likely explanation. Ex. 25, Pinto-Martin Dep. Tr. at 123:7–12 (agreeing that "the most likely explanation is causation"); Ex. 31, Faraone Dep. Tr. at 404:14–405:19 ("Valproate['s]…associat[ion] with higher incidence[s] of autism….rings a bell."); Ex. 26, Chung Dep. Tr. 310:15–20 (identifying "in utero exposure to valproic acid" as a "cause[] of autism.").[19] If reasonable experts can conclude that exposure to valproic acid causes ASD and ADHD based on a handful of observational studies (and in the face of all the same theoretical confounders at issue in this case), it follows *a fortiori* that reasonable experts can find a causal relationship based on the wealth of studies suggesting causation between APAP and ASD and ADHD.

B. The Second Circuit Holds Expert Testimony Is Allowed Based on Far Less Evidence.

The asbestos-colorectal cancer litigation is instructive. *See In re Joint E. & S. Dist. Asbestos Litig.*, 52 F.3d 1124 (2d Cir. 1995) ("*Joint Eastern II"*). In the early 1990s, a debate arose about whether asbestos could cause colorectal cancer. The evidence was decidedly mixed.[20] There were *numerous* studies showing no association between asbestos exposure and colorectal

between prenatal valproate exposure and offspring ADHD symptoms." *Id*. at 8. And the authors of the Christensen study noted that, at the time, "previous studies showed no clear evidence" of ADHD risk. *Id*. at 2. The causal inference was thus based on deeply conflicting results that were at best "moderate" in magnitude.

[19] Defendants make this false claim about valproic acid multiple times in their brief. Indeed, their opening paragraph says "[A]lthough some environmental exposures have been associated with an increased risk for ASD, none has been established as causal." Defs. ASD Br. at 1.

[20] As one researcher put it in 1990, "since [1964], a large number of historical cohort studies of workers exposed to asbestos have been reported; some show an elevated mortality from colorectal cancer while others do not." Ex. 61, Weiss (1990) at 876. And although "[e]arly reviews favored a cause and effect relationship," "as more information …accumulated, recent reviewers…most commonly stated that an assessment of causality is inconclusive or negative." *Id.* During the litigation, the Court acknowledged as much, stating that (in 1995) "[t]he scientific community is divided on whether asbestos exposure significantly increases the risk of contracting colon cancer." *Joint Eastern II.*, 52 F.3d at 1126.

cancer. *See, e.g.*, Ex. 60, Garabrant (1992) at 843 ("[O]ccupational exposure to asbestos is not a risk factor for colon cancer"); Ex. 61, Weiss (1990) at 877 (finding that eleven cohort studies analyzed did not show a statistically increased risk); Ex. 78, Edelman (1988) at 75 (examining "32 independent cohorts of asbestos workers" and finding "[n]o consistent evidence . . . to indicate that exposure to asbestos increases the risk of gastrointestinal cancer"). A full ten studies had shown risk ratios below 1.0, indicating that asbestos exposure *protected against* colon cancer. *See In re Joint E. & S. Dist. Asbestos Litig.*, 827 F. Supp. 1014, 1042 n.38 (S.D.N.Y. 1993) ("*Joint Eastern I"*) (collecting these studies). The animal data did not provide compelling evidence of a link, showing at best "inconclusive evidence . . . of carcinogenicity." Ex. 60 Garabrant (1992) at 844; *see also* Ex. 61, Weiss (1990) at 883 ("[T]here is no support for the hypothesis of causality from animal experiments.").[21]

Authors working on the asbestos/colon-cancer link conducted their own Bradford Hill analysis. They determined that "[c]onsistency" is "not met," that "dose-response" "has not been demonstrated," that "[s]pecificity cannot be demonstrated," and that "there was a lack of coherence" for the hypothesis. *Id.* at 882–83. The plaintiff's experts were nonetheless permitted to opine that asbestos causes colorectal cancer. The jury verdict went in the plaintiff's favor, but the district granted defendants' post-trial judgment as a matter of law. *Joint Eastern I*, 827 F. Supp. at 1051. The Second Circuit then reversed the district court's determination that the causation evidence was insufficient. *See Joint Eastern II*, 52 F.3d at 1126 ("We believe that the

[21] The Occupational Safety and Health Administration (OSHA) and Environmental Protection Agency (EPA) had made statements linking asbestos to gastrointestinal cancers *generally*. *See* Occupational Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite, 51 Fed. Reg. 22620, 22612 (June 20, 1986) (codified at 29 C.F.R. pts. 1910, 1926); Asbestos; Manufacture, Importation, Processing, and Distribution in Commerce Prohibitions, 54 Fed. Reg. 29461, 29469 (July 12, 1989) (codified at 40 C.F.R. pt. 763). At the time, however, asbestos was not considered a risk factor for colorectal cancers specifically by medical leading authorities. *See Cancer Facts & Figures—1992*, Am. Cancer Soc'y, 8 (1992); Jean D. Wilson et al*., Harrison's Principles of Internal Medicine* 1289 (12th ed. 1991).

district court overstepped the boundaries of the role contemplated by *Daubert* and inappropriately usurped the role of the jury.").

C. FDA's Reviews Provide No Basis for Exclusion.

Defendants have repeatedly tried to use the federal government as a shield, unsuccessfully arguing preemption before, Dkt. 56, and now sprinkling in references to the DOJ submission throughout their briefs. But not even Defendants can bring themselves to suggest that the government's statements supply *legal* grounds for excluding Dr. Baccarelli. Nor could they. As the United States said, it is "[o]f course" for this Court and this Court alone "to review the admissibility of expert and other evidence in these matters." Dkt. 1105 at 1 n.1. That expert inquiry is guided exclusively by Rule 702 and the binding precedent construing it. *See Bair Hugger*, 9 F.4th at 789 (reversing district court's grant of *Daubert* motions even though the FDA had made a determination that it could not "identify a consistently reported association").

Nothing in the government-provided materials supplies factual grounds for excluding Dr. Baccarelli under Rule 702, either. In Defendants' telling, FDA has definitively "rejected the notion that [APAP] is *capable of* causing either ASD or ADHD in children." Defs. ASD Br. at 68 (emphasis added). What the United States *actually* said was that one of their epidemiology divisions reviewed (three) new studies in March 2023 and decided that "[t]he three studies reviewed here are limited and do not change [the division's] conclusions from its most recent review" of November 2022. Dkt. 1105-1 at 17. It is not clear whether anyone at FDA actually read Plaintiffs' letter. And it *is* clear that *nobody* from the United States reviewed the totality of the evidence, including the experts' reports, depositions, and supporting studies. Dkt. 1105.[22]

[22] That is hardly Plaintiffs' fault. From the beginning of this litigation, Plaintiffs have invited everyone who wishes—including the federal government—to review the compelling body of evidence produced by Plaintiffs' experts. It was Defendants who urged the FDA not to look at that evidence. Dkt. 794. Their wish was granted.

The earlier FDA reviews in fact *demonstrate* that reasonable epidemiologists can opine as Dr. Baccarelli has. In 2016, epidemiologists *within FDA* stated that "[w]ith growing evidence for adverse neurodevelopmental outcomes being associated with in utero APAP exposure, even in the absence of *proof of* a causal relationship, it would be appropriate for FDA to bring this issue to the attention of consumers and health care providers through one of the communication avenues available to the agency." Dkt. 483-1 at FDACDER000014 (emphasis added). Among the "essential points" that these FDA scientists wished to "communicate" were that "the current data raise the possibility of neurodevelopmental harm to the fetus from maternal APAP use." *Id.* There would be no reason to do that if (as Defendants would have the Court believe) the science conclusively shows that these associations are the result of confounding or that APAP is not even "capable of" causing ASD or ADHD. Defs. ASD Br. at 68.

Later statements by those at FDA confirm that Dr. Baccarelli's opinion is hardly derived from "junk science." *Amorgianos*, 303 F.3d at 267. In May 2022, the National Center for Toxicological Research convened a Science Advisory Board Meeting at which Dr. John Talpos, Director of the Division of Neurotoxicology, stated that the concerns about "in utero exposure to acetaminophen, as highlighted by [the] 2021 consensus statement," are based on "a series of *high-quality* epidemiological studies" with "really very big" "cumulative sample sizes" that employed "an impressive data set highlighting this potential concern." Ex. 123, NCTR Tr. at 36 (emphasis added). In July 2022, the FDA admitted that the epidemiology was as good as it was going to get, stating that "it is unlikely that further observational studies will provide more clarity without more mechanistic data." Dkt. 483-1 at FDACDER000114.

FDA itself is not of one mind. But even if it were, its views have no bearing on the *Daubert* question for at least two reasons. The first is the obvious one: "[t]he focus" of *Daubert* "must be

solely on principles and methodology, not on the conclusions they generate." 509 U.S. at 595. That FDA reached a different "conclusion" on whether causation has been established says nothing about Dr. Baccarelli's "principles and methodology" in finding causation is most likely.

Second, as this Court has recognized, "[i]t is a 'central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." Dkt. 145 at 7 (quoting *Wyeth v. Levine,* 555 U.S. 555, 579 (2009)). As a result, "state law offers an additional, and important, layer of consumer protection that complements FDA regulation." *Wyeth*, 555 U.S. at 579. The reason state tort law plays such a vital role is not because FDA lacks competence, but rather because the agency "has limited resources to monitor the 11,000 drugs on the market." *Id.* at 578. As a result, FDA is often slow to address risks. APAP itself provides a vivid example. Since the late *1960s*, APAP has been associated with severe liver injuries via case reports and animal studies.[23] A 1975 editorial in *The Lancet* suggested that researchers should look for an alternative pain reliever "which cannot cause liver damage,"[24] and by the mid-1990s, APAP was the most common cause of acute liver failure in the United States.[25] The FDA finally *began* examining the problem in earnest in the 1990s, "when the scope of the problem became evident,"[26] and it convened an advisory committee in 2002. Ex. 76, Woodcock Testimony at 17. Despite all this—and despite work on the liver warning being a "very high priorit[y]" for the agency—FDA did not mandate a label change until 2009. *Id.* It did so in the face of JJCI's predecessor's strenuous opposition, with rhetoric that will sound familiar to the Court: a hepatoxicity warning was "unnecessary and serves only to confuse and frighten the vast majority of consumers who use

[23] William M. Lee, M.D., *Acetaminophen Toxicity: A History of Serendipity and Unintended Consequences*, 16 Clinical Liver Disease 34, 35 (2020).

[24] *Id.* at 42 (quoting *Editorial: Paracetamol Hepatoxicity*, Lancet (1975)).

[25] *Id.* at 38, 41.

[26] Prescription Drug Products Containing Acetaminophen; Actions to Reduce Liver Injury From Unintentional Overdose, 76 Fed. Reg. 2693 (Jan. 14, 2011).

acetaminophen in a rational and appropriate fashion." *See* Ex. 75, Propublica (2013). The 2009 warning language was nearly identical to that proposed by the advisory panel *32 years* earlier. *Id*. As Senator Grassley wrote in 2007, "for years since the Advisory Committee identified the public safety need"—and decades after the risk was first identified—FDA has still "not implemented measures to protect the public" by mandating a warning.[27]

FDA action on the cold medicine phenylephrine provides a more recent example. In 2006, researchers sent a citizen petition to the FDA providing data demonstrating that phenylephrine worked no better than a placebo.[28] Those researchers encountered a "chronically understaffed and underfunded FDA,"[29] in particular a "beleaguered over-the-counter division, which had [just] 31 staff members."[30] When FDA finally convened an advisory committee, it unanimously found a few weeks ago that oral phenylephrine is ineffective. Even now, no formal action has been taken.

IV. Dr. Baccarelli's Methodology

Dr. Baccarelli's report spans 174 pages plus nearly 20 pages of references and 20 pages of tables transparently demonstrating his assessment of the epidemiological literature. He first provided an overview of his methods, Ex. 1, Baccarelli Rep. at 12–30, explained the relevant features of APAP, ASD, and ADHD, *id.* at 30–44, described the evidence on APAP's mechanism of action, *id.* at 44–51, and explained basic epidemiological concepts. *Id.* at 51–79.

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[27] Press Release, U.S. Senate Comm. on Fin., *Grassley Urges FDA to Educate and Inform Public About Acetaminophen* 3 (Mar. 20, 2007),https://www.finance.senate.gov/ranking-members-news/sen-grassley-urges-fda-to-educate-and-inform-public-about-acetaminophen.

[28] Randy C. Hatton et al., *Efficacy and Safety of Oral Phylephrine: Systematic Review and Meta-Analysis*, 41 Annals Pharmacotherapy 381–90 (April 2007); *see also* Leslie Hendeles & Randy Hatton, *Letter to the Editor—Oral Phenylephrine: An ineffective Replacement for Pseudophedrine?*, 18 J. Allergy & Clin. Immunology 1 (July 2006).

[29] Haley Weiss, *With the Decongestant SNAFU, the FDA Tries Something New*, Time (Sept. 14, 2023), https://time.com/6314120/fda-decongestant-phenylephrine-decision/.

[30] Christine Jewett, *Why the F.D.A. Took So Long to Tackle a Disputed Cold Remedy*, N.Y. Times (Sept. 15, 2023), https://www.nytimes.com/2023/09/15/health/fda-cold-medicine-decongestant.html.

A. Dr. Baccarelli's Review of the Literature

Dr. Baccarelli then proceeded to describe the evidence regarding the link between prenatal APAP exposure and NDDs. Although Defendants accuse Dr. Baccarelli of "conflat[ing] ADHD and ASD, which have distinct sets of diagnostic criteria," Defs. ASD Br. at 45, Dr. Baccarelli's review of the literature did no such thing. He considered the ADHD and ASD literature separately. His report first summarizes "the association between prenatal acetaminophen and ADHD." Ex. 1, Baccarelli Rep. at 79–97. Dr. Baccarelli then turns to the ASD literature. *Id.* at 97–104. After reviewing these two bodies of ADHD and ASD literature separately, Dr. Baccarelli reviewed the research on "other neuropsychological and developmental disorders." *Id.* at 105–12.

When reviewing this literature, Dr. Baccarelli did not just highlight the strengths of the studies but also candidly flagged the limitations.[31] To take an example from the ADHD literature, although Dr. Baccarelli viewed the Liew (2014) paper as a study that "strongly supported the association between prenatal acetaminophen and ADHD," Ex. 1, Baccarelli Rep. at 81–82,[32] he nevertheless was careful to describe its limitations—in particular, the "use of telephone-based interviews," "the possibility of selection bias," and "the theoretical possibility of unmeasured confounding." *Id.* at 81.[33] To take an example from the ASD literature, Dr. Baccarelli considered the Liew (2016a) study to be especially persuasive. But he nevertheless made clear that the study

[31] Defendants' experts, by contrast, were often not so even-handed in their assessment. Defendants' primary study is Gustavson (2021), a sibling-control analysis that has many limitations—most notably small sample size—that its own authors flagged as serious concerns. But in describing the Gustavson (2021) study, Dr. Pinto-Martin concealed the sample-size problem by "omitting" the relevant sample size from her report. Ex. 25, Pinto-Martin Dep. Tr. at 432. And more generally, Dr. Pinto-Martin did not describe *any* limitations of that study. *Id.* at 434:3–18. As she put it, "I do not critique Gustavson." *Id.* at 436:16.

[32] Although Defendants now criticize that study, [redacted]

[33] To take another ADHD example, when describing the Avella-Garcia (2016) study, Dr. Baccarelli flagged the fact that it evaluated "ADHD symptoms" (rather than diagnoses) and described other "major limitation[s]" of that study, including its "modest sample size," inability to "evaluate . . . dosage," and difficulty of evaluating ADHD at the young age—"4.8 years"—at which the children were assessed. Ex. 1, Baccarelli Rep. at 83.

had its flaws as well: "lack of direct measure of exposure," "lack of precise measurement of acetaminophen dose," and "the theoretical possibility of residual confounding." *Id.* at 99.

Although Defendants repeatedly accuse Dr. Baccarelli of "fail[ing] to acknowledge" or "dismiss[ing]" studies' limitations, Defs. ASD Br. at 32, 42; Defs. ADHD Br. at 21, his report reveals the opposite: he faithfully, carefully, and candidly summarized the strengths *and* weaknesses of the various studies—and then explained how they affected his analysis in this case.[34] Dr. Baccarelli's analysis of the Gustavson (2021) paper illustrates this point vividly, as it is Defendants' singularly preferred study. Dr. Baccarelli acknowledged the purpose of the study: "to assess the confounding effect of maternal/familial factors, including genetics." Ex. 1, Baccarelli Rep. at 117. He accurately described the results: a non-statistically significant association between prenatal APAP and ADHD when the sibling controls were employed. *Id.* at 118 ("HR = 1.06 (95% C.I. = 0.51–2.05)"). He even quoted the authors' statement about what the results might mean—"the authors concluded that the analysis revealed a 'substantial family effect' that 'suggested that unmeasured familial confounding factors may explain at least part of the observed association between maternal long-term acetaminophen use and ADHD in the child'"—even though these statements hardly bolstered his overall opinion. *Id.* Dr. Baccarelli did not hide the ball. He then went on—for five full pages in his main report and another three in his rebuttal report—to explain in great detail why Gustavson did not change his overall assessment in light of the study's serious limitations, all of which were also flagged by the Gustavson authors themselves. *Id.* at 118–23, Ex. 6, Baccarelli Rebuttal Rep. at 6–7.

[34] For example, Defendants claim that Dr. Baccarelli did not "address the [Ji (2020)] authors' warning that they were 'unable to exclude the potential residual confounders because of unmeasured genetic and environmental factors.'" Defs. ASD Br. at 29. That is simply false. On page 90 of his report, Dr. Baccarelli states explicitly that one limitation of the Ji (2020) study is "the theoretical possibility of residual confounding." Ex. 1, Baccarelli Rep. at 90.

B. Dr. Baccarelli's Bradford Hill Analysis

Dr. Baccarelli proceeded to conduct a Bradford Hill analysis. Even Defendants admit this was a valid method. Defs. ASD Br. at 47. When evaluating the nine Bradford Hill factors, Dr. Baccarelli did not uncritically ignore the limitations. He candidly admitted that "the specificity criterion is not satisfied here." Ex. 1, Baccarelli Rep. at 162 ("In my view, the specificity criterion is not satisfied here."). For the strength criterion, he cautiously described many of the associations as "moderate." *Id.* at 159. As to consistency, he admitted that "there are some null results in the literature, *i.e.*, studies that did not show a statistically significant association," rather than attempting to say that the literature was unanimous in showing a risk. *Id.* at 161.[35] Dr. Baccarelli (correctly) noted that the vast majority of studies that looked for dose response had demonstrated one. He nevertheless flagged that "one study did not show a dose response" for reduced IQ. *Id.* at 163. And for the experiment criterion, he conceded that there were no "experimental studies in humans" due to ethical concerns. *Id.* at 167.

After factoring in these limitations, Dr. Baccarelli was still able to make a causal inference based on the weight of the evidence. As Dr. Baccarelli pointed out, with the exception of temporality, none of the factors are *required* before making a causal inference. *See* Ex. 35, Ref. Manual at 600 ("One or more [BH] factors may be absent even when a true causal relationship exists."). Dr. Baccarelli went on to explain exactly what role each factor played in his analysis—and indeed what weight he gave each factor. For example, Dr. Baccarelli "weighed dose response strongly in favor of causation" given the numerous dose-response results in the literature and the

[35] In light of this candid description of the literature, Defendants' accusation that Dr. Baccarelli has engaged in a "result-oriented dismissal of statistical significance" is truly a surprising one. Defs. ASD Br. at 54. Dr. Baccarelli did not "dismiss" statistical significance—indeed, he typically described non-significant results as "null." Ex. 1, Baccarelli Rep. at 161. What Dr. Baccarelli *did* say is that a *set* of results is "consistent" even if some results are not statistically significant. But that is exactly what the authoritative textbook in the field says as well. Ex. 63, Modern Epidemiology at 66.

fact that Bradford-Hill himself stated that dose response "adds a very great deal" in favor of causality. Ex. 1, Baccarelli Rep. at 168. He also placed great emphasis on "strength" because "studies that use objective measures of exposure demonstrate both biologic gradient and risk estimates that are more than double," *i.e.*, risk ratios of greater than 2.0. *Id.* at 169. Dr. Baccarelli gave "consistency a great deal of weight in favor of causality" because the increased risk has been demonstrated "across many different study designs and populations," *id.* at 169—again, exactly what Bradford Hill himself said to look for. Ex. 69, Bradford Hill at 8.

Dr. Baccarelli also made clear which factors he gave less weight—and exactly why he did so. He placed little weight on the analogy criterion, even though it was satisfied, because it often proves too much: "sometimes analogous drugs do not have analogous effects." Ex. 1, Baccarelli Rep. at 170. Similarly, he placed little weight on specificity because it often is not satisfied even though an agent is causal, *e.g.*, the link between tobacco and cancer. *Id.* at 168. For coherence, he weighed it less strongly—again, even though the criterion was satisfied—because ASD and ADHD are "believed to have many causes and possibly many pathways of injury." *Id.* at 169. And for experiment and biological plausibility, he gave them minor and moderate weights because they merely "corroborate" what is evident from the epidemiology literature itself. *Id.* at 169–70. After extensively and critically discussing these factors—both the ones that were and were not satisfied—Dr. Baccarelli ultimately concluded that "prenatal use of acetaminophen exposure can cause the offspring to develop NDDs such as ADHD and ASD." *Id.* at 170.[36]

[36] In their briefs, Defendants suggest that Dr. Baccarelli did not perform a separate Bradford Hill analysis for ADHD, ASD, and NDDs generally. Defs. ASD Br. at 48. That is not true. Dr. Baccarelli stated that he "performed a Bradford-Hill assessment separately for ASD, ADHD, and the constellation of neurologic deficits identified in my Navigation Guide assessment." Ex. 1, Baccarelli Rep. at 170. Although, to avoid repeating the factors three times over, he discussed the Bradford Hill factors only once, Dr. Baccarelli summarized the ASD, ADHD, and NDD literature entirely separately. He also performed a full-blown Navigation Guide analysis separately.

C. Dr. Baccarelli's Navigation Guide Analysis

In addition to the Bradford Hill analysis, Dr. Baccarelli also employed a method referred to as the "Navigation Guide," which is based on a long-standing methodology called "GRADE" that is used to evaluate the quality of evidence from clinical trials. Dr. Baccarelli performed this analysis separately for ASD, ADHD, and NDDs more generally. *Id.* at 139–46 (ADHD); *id.* at 146–52 (ASD); *id.* at 152–58 (other NDDs). The Navigation Guide provides an objective set of criteria—defined in advance—that researchers can use to grade the strength of studies "including observational and preclinical studies, to assess a causal relationship." *Id.* at 12. It also lays out the analysis in a transparent and accessible way so that a reader can clearly understand how each study was reviewed, weighted, and included in the overall analysis.[37] Dr. Baccarelli began his Navigation Guide analysis by conducting a systematic search of the literature to identify all published literature regarding the association between ADHD, ASD, and NDDs. *Id.* at 13.[38] Dr. Baccarelli then extracted the type of data specified by the Navigation Guide. *Id.* at 14. Using the GRADE system—"another systematic approach to grade quality of evidence"—Dr. Baccarelli systematically assessed the risk of potential bias. *Id.* at 14–19.

In making these assessments, Dr. Baccarelli provided pre-defined criteria by which he was judging the studies. For example, to evaluate whether a study was prone to confounding, Dr. Baccarelli stated that he would rate a study as having a "low risk of bias (score = 1)" if it "considered and appropriately adjusted for confounding"; would rate a study as "probably low risk of bias" (score = 2)" if it "adjusted for multiple potential confounding variables but did not

[37] In this way, it is the opposite of the kind of analysis employed by the epidemiology expert in *Mirena*, who employed a "black box" approach to "Bradford Hill review" that prevented others from being able to "validate or check his work." *Mirena*, 341 F. Supp. 3d at 249.

[38] In his report, Dr. Baccarelli specifically identified the search terms he used, allowing other scientists to be able to replicate his methodology. Ex. 1, Baccarelli Rep. at 13–14.

assess/control for confounding by indication"; would rate a study as "probably high risk of bias (score = 3)" if it "did not evaluate a comprehensive list of confounders," and would rate a study as "high risk of bias" (score = 4)" if it "did not consider/adjust for confounding variables or used inappropriate methods for confounding control." *Id.* at 18.

Dr. Baccarelli also graded the "strength of evidence of each study." *Id.* at 19. Again using pre-defined criteria, he scored the studies based on their size, whether the effect was large, whether there was a dose response, whether the study had internal consistency, whether the study had adequately controlled for bias, and a catch-all category. *Id.* at 19–21. Dr. Baccarelli then used these scores to grade the strength of evidence of each study numerically. *Id.* at 22.

When applying the Navigation Guide, Dr. Baccarelli was candid about where the evidence was particularly compelling, and where it was less so. For confounding, Dr. Baccarelli gave elevated bias scores (Score 2, "probably low risk of bias") to studies that "did not control for confounding by indication." *Id.* at 141, 147.[39] And for exposure assessment, Dr. Baccarelli gave elevated bias scores to studies that used questionnaires to measure APAP exposure—and gave a "high risk of bias" score to one study whose exposure measurements appeared to be out of line with other facts known about APAP use rates. *Id.* at 140. The same is true for Dr. Baccarelli's evaluation of the strength of the studies. As he did with his Bradford Hill analysis, Dr. Baccarelli conceded that most of the studies showed only a "moderate effect size" and thus gave them a score of 0. It was only the studies that showed effects of greater than 2.0 that received the higher score of +2 for effect size. *Id.* at 143, 150. Based on this Navigation Guide analysis, Dr. Baccarelli

[39] Dr. Baccarelli also gave a reasoned explanation for not assigning an even higher bias score: The studies that *did* evaluate confounding by indication found no evidence of it, suggesting that the studies that did not control for confounding by indication "probably"—though not definitely—were not affected by confounding by indication. *Id.* at 141.

made a final, separate determination as to the evidence of a causal link between prenatal APAP exposure, ADHD, ASD, and other NDDs. *Id.* at 145 (ADHD); *id.* at 151 (ASD).

D. Dr. Baccarelli Relied on Prior Reports Only as Background Material.

Defendants suggest that Dr. Baccarelli "cut and pasted" congressional-hearing testimony from Dr. Anne McTiernan. He did not. Dr. Baccarelli is not a professional witness. In order to show him how expert reports are typically structured, Plaintiffs' counsel provided him with a report from Dr. McTiernan. Dr. Baccarelli then used that report as a template for his background sections. The similarities that Defendants identify are not substantive. For example, they fault him for saying that the "foundation of this report" is his education, experience, and prior work in terms too similar to Dr. McTiernan's. This is neither substantive nor nefarious. And if the Court is interested in examples of copying, however, it need look no further than Defendants' briefs and experts. Entire passages of Defendants' briefs are lifted near-verbatim from Dr. Pinto-Martin's expert report.[40] The Court should ignore this sideshow.

LEGAL STANDARD

The purpose of *Daubert* is to exclude "junk science," *Amorgianos*, 303 F.3d at 267, *i.e.*, "unreliable nonsense opinions," *Alaska Rent-A-Car, Inc. v. Avis Budget Grp., Inc.*, 738 F.3d 960, 969 (9th Cir. 2013). "It is not the role of the district court to make ultimate conclusions as to the persuasiveness of the proffered evidence." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). Nor may the district court evaluate "the persuasiveness of competing scientific studies," *id.*, or "[take] sides on questions that are currently the focus of extensive scientific research and debate," *Milward*, 639 F.3d at 15, 22. *Daubert* "was never intended to keep from the jury the kind of evidence scientists regularly rely on in forming opinions

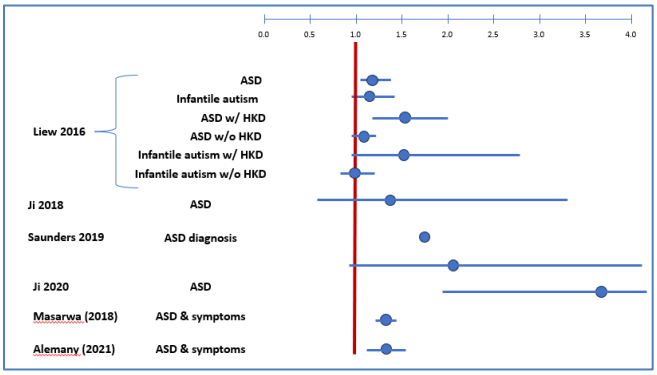
[40] *Compare* Defs. ADHD Br. at 43 *with* Ex. 13, Pinto-Martin Rep. at 93–94; *compare* Defs. ADHD Br. at 42 *with* Ex. 13, Pinto-Martin Rep. at 55; *compare* Defs. ASD Br. at 2–3 *with* Ex. 13, Pinto-Martin Rep. at 45.

of causality simply because such evidence is not definitive." *Id.* A "minor flaw" in an expert's method is not enough for exclusion: the flaw must be "large enough that the expert lacks 'good grounds' for his or her conclusions." *Amorgianos*, 303 F.3d at 267 (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 746 (3d Cir. 1994)). Only when the conclusion is connected to the data by "ipse dixit" alone—and nothing else—may an expert be excluded. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997); *Bair Hugger*, 9 F. 4th at 778 ("[A] district court may exclude an expert's opinion [only] if it is so fundamentally unsupported by its factual basis that it can offer no assistance to the jury.").[41]

ARGUMENT

I. Dr. Baccarelli Reasonably Concluded That There Is an Association Between Prenatal APAP Exposure and ASD.

Defendants' primary argument against Dr. Baccarelli undermines their credibility. They spend 20 pages claiming that Dr. Baccarelli could not reasonably conclude there is an *association* between prenatal APAP exposure and ASD. Defs. ASD Br. at 27–47.[42] But a picture is worth a thousand words.



[41] Defendants argue that the Court must take a "hard look" at Dr. Baccarelli's methodology in part because his opinion regarding APAP has not "been subjected to peer review or publication." Defs. Mechanism Br. at 10, Dkt. 1165. Dr. Baccarelli testified that he was planning to publish a "condensed" version of his expert report as it was "something important for the literature." Ex. 20, Baccarelli Dep. Tr. at 58:22–59:7. Defense counsel then inappropriately stated that he was "very sure there's zero percent chance" of it being published. *Id.* at 59:12–18. Nevertheless, Dr. Baccarelli is currently in the process of getting it published.

[42] In Defendants' ADHD brief, they do *not* argue against an association.

As Defense expert Dr. Pinto-Martin admitted, all but one of the original papers shown here (a subgroup in a single study) show that "the woman who was exposed to APAP, or in this case more APAP, had a higher rate of having a child with ASD." Ex. 25, Pinto-Martin Dep. Tr. at 262:21–263:22. The two meta-analyses only bolster that pattern. Defendants do not explain why it would be "junk science" for an expert like Dr. Baccarelli to believe his own eyes. "An association between exposure to an agent and disease exists when they occur together more frequently than one would expect by chance." Ex. 35, Ref. Manual at 566. And not even Defendants' experts suggested that *all* of these results could be chance findings. Ex. 25, Pinto-Martin Dep. Tr. at 176:19–177:6 ("[C]hance was not my primary objection to the credibility of the results where there was a reported increased risk."); *id.* at 180:21–182:3.

Moreover, Defendants conspicuously fail to mention that there is a time-honored method of determining whether there is an association (overall) across a body of literature: meta-analysis. As the Federal Reference Manual notes, the "scientific record" often includes "a number of epidemiologic studies whose findings differ," either because "one [study] shows an association and [another] does not" or because they "report associations, but of different magnitude." Ex. 35, Ref Manual at 606–07. Because "studies may disagree," "the technique of meta-analysis was developed" as a way to "represent the totality of the studies reviewed." *Id.* at 607. There are *two* meta-analyses of extremely large size—Masarwa and Alemany—and both reported a statistically significant association for the ASD literature they reviewed. Ex. 65, Masarwa (2018) at 1822, Ex. 37, Alemany (2021) at 1000. That puts to rest any notion that Dr. Baccarelli should not have viewed this literature as showing an association.

A. Numerous Independent Scientists Have Recognized the Association.

It is no surprise that Dr. Baccarelli's opinion is shared by independent scientists. The Ji (2020) authors stated that "ecologic and cohort studies have found an association between maternal

acetaminophen use and risk of . . . ASD." Ex. 46, Ji (2020) at 181. The Alemany authors stated that their "findings provide support for the association between prenatal acetaminophen and [autism] symptoms in line with a previous meta-analysis." Ex. 37, Alemany (2021) at 1000. And the Masarwa authors stated that "acetaminophen exposure during pregnancy is associated with" a "20% increased risk of ASD." Ex. 65, Masarwa (2018) at 1822. In their briefs, Defendants have identified *zero* pieces of literature stating the opposite, *i.e.*, saying that a literature-wide association has *not* been observed. Only (some of) their experts even make this claim in the context of this litigation.

B. The Limitations of the Studies Do Not Undermine the Association.

Defendants say that Dr. Baccarelli did "not account for significant limitations" in the Ji (2020) and Liew (2016a) study. Defs. ASD Br. at 27. That is simply false. Dr. Baccarelli described, analyzed, and exhaustively "accounted for" the limitations in the Ji (2020) study—including *all of* the limitations that Defendants point to in their brief. All of them. *Compare* Defs. ASD Br. at 28 ("Ji (2020) measured acetaminophen in maternal and umbilical cord blood samples at the time of birth"), *with* Ex. 1, Baccarelli Rep. at 90 ("Limitations of this study include the ability to measure acetaminophen levels in the umbilical cord at only one point in time [at the time of birth]"); *compare* Defs. ASD Br. at 28–29 ("Another challenge with interpreting Ji (2020) is that all the umbilical cord samples in the study contained acetaminophen"), *with* Ex. 1, Baccarelli Rep. at 90 ("Limitations of this study include . . . 100% detection of acetaminophen in the sample."); *compare* Defs. ASD Br. at 29 ("[N]one of plaintiffs' experts addresses the [Ji (2020)] authors' warning that they were "unable to exclude the potential residual confounders"), *with* Ex. 1, Baccarelli Rep. at 90 ("Limitations of this study include . . . the theoretical possibility of residual confounding.").

Dr. Baccarelli also faithfully described and analyzed the limitations in the Liew (2016a) study—once again, including *all of* the limitations that Defendants point to in their brief. *Compare* Defs. ASD Br. at 31 (pointing out that the Liew (2016a) paper "only found a statistically significant association for ASD with [hyperkinetic disorder]"), *with* Ex. 1, Baccarelli Rep. at 99 ("Prenatal acetaminophen was more strongly associated with ASD accompanied by hyperkinetic symptoms … but not with other ASD.")[43]; *compare* Defs. ASD Br. at 32 ("Liew (2016) cautioned that 'residual confounding by indication or genetic factors [are] alternate explanations'"), *with* Ex. 1, Baccarelli Rep. at 32 ("Limitations include . . . the theoretical possibility of residual confounding.").

In any event, the limitations of these two studies have no bearing on whether they showed an association. Defendants claim that it would be a "misreading" of Ji to claim it shows "an association" between prenatal APAP and ASD. Defs. ASD Br. at 28. The Ji authors disagree: "In this study, cord biomarkers of fetal exposure to acetaminophen were associated with significantly increased risk of childhood . . . ASD in a dose-response fashion," thereby providing "support [for] previous studies regarding the association." Ex. 46, Ji (2020) at 188. The same is true for Liew (2016a). Although Defendants point to statements by the authors about the theoretical possibility of "residual confounding," Defs. ASD Br. at 32, confounding is only a possibility *to explain an association*. Ex. 35, Ref Manual at 591. That is why, once again, the study authors agree with Dr. Baccarelli: "prenatal exposure to acetaminophen was associated with a higher risk for ASD and

[43] Defendants falsely claim that "none of plaintiffs' other experts [other than Dr. Cabrera]" addresses this limitation—*i.e.,* that the Liew (2016a) paper did not find a statistically significant for ASD without hyperkinetic disorder. Defs. ASD Br. at 32. But it is there in black and white in Dr. Baccarelli's report—twice. Ex. 1, Baccarelli Rep. at 98 ("Liew et al. (2016) found that 'prenatal use of acetaminophen was associated with an increased risk for ASD in the offspring among those also diagnosed with a hyperkinetic disorder.'") (quoting Liew (2016a)); *id.* at 99 ("Prenatal acetaminophen was more strongly associated with ASD accompanied by hyperkinetic symptoms . . . but *not with* other ASD.") (emphasis added).

infantile autism in children." Ex. 45, Liew (2016a) at 953. Defendants' "ex post facto dissection[s]" of the literature showing an association "fails to undermine its reliability." *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1240 (W.D. Wash. 2003) (citing and quoting Ex. 35, Ref Manual).

Although framed as an argument about whether there is an "association," Defendants' *real* argument seems to be this: When study authors identify possible alternative explanations for their results, it is *per se* unreasonable for a scientist to make a causal inference. That fundamentally misunderstands what Dr. Baccarelli did. He did not make his causal inference on the basis of Ji (2020) or Liew (2016a) alone. Instead, he reviewed all of the epidemiology literature—along with studies showing biologic plausibility—and thereby determined that causation was most likely. The fact that an individual study suggested theoretical alternative explanations for that individual study's results says nothing about what the entire body of literature shows.

Defendants' criticism of Dr. Baccarelli's treatment of Liew (2016a) provides a vivid illustration of this issue. Defendants point out that Liew (2016a) "did not control for genetics" and thus accuse Dr. Baccarelli of "dismiss[ing] express warnings by a study's author that confounding factors might explain the reported result." Defs. ASD Br. at 32 (citing *Daniels-Feasel*, 2012 WL 4037820, at *8). But the reason Dr. Baccarelli thinks that genetic confounding is unlikely here is not because of anything in Liew (2016a) itself. As he explained in his report, it is because of (among other things) the results from *other* studies in the literature showing no link between autism-related genes and APAP use, a prerequisite for genetic confounding. Ex. 1, Baccarelli Rep. at 123; Ex. 6, Baccarelli Rebuttal Rep. at 3. That takes the Liew authors' "express warnings" seriously—by *addressing* them.

C. The Ji 2018, Saunders 2019, and Hornig 2018 Results Do Not Undermine the Association.

Defendants also argue that there is not even an "association" because "three studies (Ji 2018, Saunders 2019 and Hornig 2018) showed no statistically significant association." Defs. ASD Br. at 33. Dr. Baccarelli discussed these results at length. Ex. 1, Baccarelli Rep. at 99–101; Ex. 6, Baccarelli Rebuttal Rep. at 12–13.

To begin with, Ji (2018) showed an association, just not a significant one: every odds ratio was positive, as the study authors recognized: the "ASD diagnosis . . . group[] had more mothers with higher levels of acetaminophen metabolites" compared to the normal-child group. Ex. 66, Ji (2018) at 5.[44] The fact that mothers with higher APAP levels had more children with ASD hardly suggests "no association." More importantly, the Ji (2018) study measured APAP levels in the mother's blood one to three days after she delivered the child, providing a highly imperfect proxy for in utero APAP exposure. As between a study that measured APAP in the baby's umbilical cord blood (Ji 2020) and a study that measured APAP in the mother's blood *days after* the baby was no longer in her body (Ji 2018), it was reasonable for Dr. Baccarelli to think that the study on the baby's cord blood provided more relevant data regarding the baby's APAP exposure. Ex. 6, Baccarelli Rebuttal Rep. at 12.[45]

As for Saunders (2019), that was a retrospective case-control study involving just 141 cases and 199 controls—a total sample size in the low hundreds. It also failed to control for virtually any confounders and selected controls differently from the cases (a major methodological flaw). *See generally* Ex. 1, Baccarelli Rep. at 100. By contrast, Liew (2016a) was a prospective cohort

[44] For ADHD, Ji (2018) showed an association *and* it was statistically significant. Ex. 66, Ji (2018) at 5.

[45] Defendants themselves seem to agree, noting that "[b]ecause acetaminophen has a 2-3 hour half-life in adults, detectable levels of acetaminophen would have reflected 'recent use'—i.e., at or near labor." Defs. ASD Br. at 10. In other words, Defendants suggest that Ji (2018) provides no data about APAP exposure in pre-labor pregnancy at all. Given the question at issue here, it cannot be unreasonable to give that kind of study less weight.

study that had sample size of more than 64,000 and numerous controls. "Retrospective studies [like Saunders]. . . are usually less accurate than prospective studies [like Liew]." Ex. 35, Ref Manual at 587; Ex. 13, Pinto-Martin Rep. at 6 ("[P]rospective cohort studies [are] considered superior to retrospective case-control studies."). It was reasonable for Dr. Baccarelli to think that a methodologically inferior study with a far smaller sample size might not be the best evidence of the association between prenatal APAP exposure and ASD.[46] Ex. 1, Baccarelli Rep. at 100–01 ("[T]he [Saunders] study quality is extremely low and the results should be weighed accordingly" due to its "retrospective case-control design" among other serious flaws).[47]

As for Hornig (2019), Defendants flail in vain. That is a study on the association between fever and ASD. It did not report the association between APAP and ASD at all. Although Hornig did show a lower ASD risk ratio for febrile women who took APAP, given that fever is a possible risk factor for ASD—and APAP reduces fever—Hornig says *nothing* about whether APAP is an independent risk factor. It is entirely plausible that APAP itself increases the ASD risk and that reduction of fever decreases the ASD risk. Hornig certainly says nothing about whether APAP increases the risk of ASD for women who take APAP for headaches, pain, and so on—as Defendants concede. Defs. ASD Brief at 37 ("[I]t is not clear whether the result reported by Hornig and his colleagues can be extrapolated to afebrile women.").

More fundamentally, Defendants are wrong to suggest that one or two non-significant results are enough to eliminate any "association." Some null findings are to be *expected* in any relationship that is studied enough times. *E.g.*, Ex. 67, Surgeon General Report at 436 (noting the

[46] On this point, Dr. Pinto-Martin agrees, describing Liew (2016a) as the "best" designed study on ASD. Ex. 25, Pinto-Martin Dep. Tr. at 21:9–16. And as she conceded, it shows an association for ASD. *Id.* at 24:3–25:3.

[47] Again, Defendants' embrace of this study is telling. In a literature involving studies of hundreds of thousands mothers showing multiple statistical significant results, Defendants are suggesting that a retrospective study of 141 autism cases shows the "truth."

Surgeon General had identified *nine* study results, including multiple meta-analyses, showing non-significant results for second hand smoke).

D. Studies on Neurodevelopmental Disorders Do Not Change the Fact That There Is an Association with Autism.

Defendants' last argument in support of the notion that there is no "association" between prenatal APAP use and ASD is that studies that looked at "symptoms" associated with autism "cannot plug the holes in the relevant epidemiology." Defs. ASD Br. at 38. There are no holes to plug. *All* of the original studies in the forest plot used ASD *diagnoses* as endpoints. *See* Ex. 38, Pinto-Martin Dep. Ex. 634. Indeed, the forest plot contains the original studies on ASD diagnoses that were summarized in Dr. Pinto-Martin's *own* report (plus the two meta-analyses she disclaimed at the bottom). Ex. 13, Pinto-Martin Rep. Part VI.B.1. But Defendants offer no explanation why a reasonable scientist, viewing the totality of the evidence, cannot also consider literature that evaluates neurodevelopmental disorders or symptoms of ASD and ADHD as endpoints. To the contrary, independent scientists routinely do so. [redacted] *See, e.g.*, Dkt. 483-1 at FDACDER000090 ("22 studies examined the association between prenatal APAP use and functional neurobehavioral outcomes"); Ex. 111, APAP-JJCI-0000525829.

To be sure, studies that focus on ASD or ADHD diagnoses as endpoints may be more probative, which goes to the *weight* to give non-endpoint studies, not relevance. Defendants pretend Dr. Baccarelli placed the same weight on studies of "language delay in girls" as he did on studies of ASD diagnoses. Defs. ASD Br. at 39.[48] They imply that he views such studies as *necessary* to establish even an association. None of that is accurate. *See* Ex. 6, Baccarelli Rebuttal

[48] They also criticize Dr. Baccarelli for relying on Liew (2016b), which measured IQ, even though he noted that using IQ as an endpoint was a limitation of the Laue (2019) study. Defs. ADHD Br. at 13. And they criticize him for stating that the CBCL was an endpoint that was not "as persuasive" as a diagnosis. *Id.* at 14. But Dr. Baccarelli *nowhere* suggested that he gave more weight (or even equal weight) to studies with non-diagnostic endpoints. He simply considered them—as a good epidemiologist should—because they are obviously relevant.

Rep. at 18 ("To be sure, studies showing an association between prenatal APAP exposure and clinical diagnoses of ADHD and ASD provide particularly powerful evidence of a causal relationship. But the power of those studies in no way suggests that researchers should blind themselves to the results from studies using other endpoints that are obviously relevant to the question at hand."). Dr. Baccarelli *separately* reviewed the studies on ASD before *separately* reviewing the studies on NDDs more generally.[49] Indeed, Dr. Baccarelli performed separate, full-blown Navigation Guide analyses on ADHD, ASD, and NDDs. Ex. 1, Baccarelli Rep. at 138–46, 146–51, 151–58. Based on his analysis of the ASD studies *alone*, he was able to conclude that there was an association.

Defendants' example that is putatively "emblematic of the problem," Defs. ASD Br. at 40, is actually emblematic of their cramped, litigation-driven definition of the relevant body of literature. Defendants breathlessly report that Dr. Baccarelli evaluated and weighed the Avella-Garcia (2016) paper, which used the Childhood Autism Spectrum Test (CAST) as an endpoint. But a study observing the results of a screening test for autism is of course *relevant* to whether an exposure causes autism. That endpoint may not be as probative as a *confirmed* ASD diagnosis,[50] but it strains credulity for Defendants to maintain that this study should have been entirely ignored. And it takes even more impudence for Defendants to contend that any epidemiologist who thinks such a study should get *some* consideration in the causal analysis is practicing "junk science."

[49] The Court should read the Defendants' citations in this section of their brief carefully. They refer the Court to "Baccarelli Rep. at 104–12" for the proposition that Dr. Baccarelli relied "heavily on so-called 'proxy' studies." Defs. ASD Br. at 38. They fail to mention that pages 104–12 are where Dr. Baccarelli includes a "summary of evidence regarding prenatal use of acetaminophen and neurodevelopmental disorders"—not ASD. Ex. 1, Baccarelli Rep. at 104. And they likewise fail to point the Court to an entirely separate and independent part of his report where he includes a "summary of evidence regarding prenatal use of acetaminophen and ASD." *Id.* at 97–104. They of course fail to mention that he performed separate Navigation Guide analyses as well.

[50] CAST is a highly validated survey instrument rivaling the best diagnostic modalities with sensitivity (true positive rate) of 100% and specificity (true negative rate) of 97%. *See, e.g.*, Ex. 174, Gharamaleki (2022).

After criticizing Dr. Baccarelli for considering these studies, Defendants proceed to consider them, chastising Dr. Baccarelli for placing *too little* weight on (certain) results. For example, Defendants accuse Dr. Baccarelli of "fail[ing] to address [the] finding" in Avella-Garcia (2016) that "girls showed significantly lower CAST scores" and that "the scores for all children were not significantly associated with in utero exposure." Defs. ASD Br. at 41. But Dr. Baccarelli specifically addresses *both* of those findings. Ex. 1, Baccarelli Rep. at 98 ("Overall, children who were ever-exposed to acetaminophen during pregnancy did not show any significant difference in CAST scores."); *id.* ("[The result for boys] differed significantly form the result found in girls, who showed a decrease . . . in CAST scores.").

Defendants next accuse Dr. Baccarelli of cherry-picking because he "downplayed" results from Leppert (2019) showing no association between APAP and ASD symptoms. But the authors of that study *themselves* "downplay" those results—they never mention them. The sub-analysis that Defendants refer to is buried in "Supplementary Table 8" in a study designed to assess the correlation between genetics and pregnancy behavior. For completeness, Dr. Baccarelli still included those results in his analysis and explained their serious limitations. But by suggesting that the Leppert paper somehow means there is no association in this literature, it is Defendants who are doing the cherry-picking. They are pulling one set of results from the supplemental tables of a study and ascribing significance to it that the study's authors never did—no surprise given that the study was not designed to evaluate that outcome.

For their last argument on this point—which, apparently, is still about whether there is an "association"—Defendants swing for the fences. They argue that it was per se "unreliable" to weigh two meta-analyses—Masarwa (2018) and Alemany (2021)—when trying to determine whether there is an association between APAP and ASD. Defs. ASD Br. at 43. Nonsense. Meta-

analyses provide *more powerful* evidence regarding an association, not less. Ex. 35, Ref. Manual at 581 n.89. The authors of those two meta-analyses disagree that their papers had nothing reliable to say on this question. Ex. 37, Alemany (2021) at 1001; Ex. 65, Masarwa (2018) at 1822. Once again, Defendants are suggesting that Dr. Baccarelli should be excluded for saying the exact same thing the study authors say.

II. Dr. Baccarelli Did Not "Ignore" or "Disregard" any ADHD Research.

A. Dr. Baccarelli Exhaustively Evaluated Genetic Confounding.

With respect to Dr. Baccarelli's opinion on ADHD, Defendants argue that he "did not consider" all the studies, that he "disregard[ed]" certain results, and that he "ignored" categories of relevant evidence. Defs. ADHD Br. at 18–19. But Defendants' *actual* complaint is not that Dr. Baccarelli failed to identify evidence that cuts against his opinion. He did that exhaustively. Their complaint is instead that he identified it, analyzed it, and ultimately did not *agree* with the interpretation Defendants prefer.[51]

That, of course, is a fatal problem for Defendants, who know perfectly well that an expert cannot be excluded merely for reaching an opinion they do not like. *See Daubert*, 509 U.S. at 595 (holding that "[t]he focus" of *Daubert* is "not on the conclusions [the experts] generate"); *Murray v. Southern*, No. C12–1854RSL, 2014 WL 8812682, at *5 (W.D. Wash Oct. 8, 2014) ("Defendants identify no reason to believe her methodology was faulty or that her testimony would be unhelpful: they simply do not like her conclusions."). So they are forced to deploy a desperate maneuver. First, Defendants draw on cases where experts *actually* ignored and disregarded conflicting lines of evidence. *See, e.g.*, *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17 CV 4188-LTS-JLC, 2021

[51] Defendants cite the Reference Manual numerous times regarding confounding and bias. But what the Reference Manual *actually* says is that "the possibility of these phenomena must be *examined*" before "any inferences about causation are drawn from a study." Ex. 35, Ref Manual at 572 (emphasis added). As detailed below, Dr. Baccarelli "examined" those possibilities in great detail.

WL 4037820 (S.D.N.Y. Sept. 3, 2021), *aff'd* 2023 WL 4837521 (2d Cir. July 28, 2023) (cited *passim* in Defendants' briefs, where the expert did not meaningfully analyze or even cite relevant studies and alternative explanations); *In re Mirena Ius Levonorgestrel-Related Prod. Liab. Litig. (No. II),* 341 F. Supp. 3d 213, 253 (S.D.N.Y. 2018) (same). Second, Defendants simply redefine what it means to "disregard" or "ignore" scientific evidence, arguing that "where a study's results *could be explained* by confounding or bias that cannot be ruled out, that result *cannot* form the basis of a reliable causation opinion." Defs. ADHD Br. at 19–20. In other words, if a study's results *could* be explained by Defendants' preferred conclusion, it is "ignoring" evidence not to reach that conclusion. If an individual study "cannot rule out" that Defendants are right, they say it is "disregarding" evidence to conclude they are wrong.

This Defendants-always-win reading of Rule 702 has never been the law. *Amorgianos*, 303 F.3d at 266 (holding that an expert need not "back his or her opinion with published studies that unequivocally support his or her conclusions"); *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1043 (2d Cir. 1995) (allowing an expert to testify even though he could not point to "a single piece of medical literature" suggesting causation); *W.R Grace*, 504 F.3d at 765 ("The study's failure to establish causation goes to the weight it should be accorded, but does not mean that an expert could not rely on it in forming an opinion."); *Milward*, 639 F.3d at 23 ("The district court erred in reasoning that because no one line of evidence supported a reliable inference of causation, an inference of causation based on the totality of the evidence was unreliable."); *In re Roundup Prods. Liab. Litig*., 390 F. Supp. 3d 1102, 1131 (N.D. Cal. 2018) (allowing an expert to testify even though he "could not definitively rule out chance, bias, or confounding"). It also flouts sound epidemiological practice. Theoretically, a study's result could *always* be due to residual confounding. Ex. 25, Pinto-Martin Dep. Tr. at 270:8–11; *see also* Ex. 35, Ref Manual at 553

("Epidemiologic methods cannot deductively *prove* causation."). The conjured standard Defendants insist upon would limit liability to *morally certain* cause-effect relationships established through unethical-to-perform randomized control trials (RCTs). Applying that rule, no reasonable expert could claim (i) that secondhand smoke causes cancer; (ii) that valproic acid causes ASD and ADHD; or (iii) in the 1960s, that smoking caused lung cancer. Every one of those associations had imperfect findings, the possibility of genetic confounding, or the possibility of residual bias. Defendants need to invent this almost-never-causal rule because Dr. Baccarelli's opinion is so well grounded under the *actual*, preponderance-of-evidence standard.

Defendants' attempt to apply their rule quickly reveals the word game it entails. They claim Dr. Baccarelli "failed to properly account for" genetic confounding in the ADHD literature, which they call "the elephant in the room." Defs. ADHD Br. at 24.[52] But Dr. Baccarelli grabbed that elephant squarely by the tusks. Across twelve pages in his original report—and ten pages more in his rebuttal report—Dr. Baccarelli explained exactly why, based on the data across *all of* the studies, genetic confounding was not the most likely explanation for the association. *See* Ex. 1, Baccarelli Rep. at 112–24 ("Special Techniques Used to Assess Unmeasured and Genetic Confounding"); Ex. 6, Baccarelli Rebuttal Rep. at 2–11. Defendants and their experts are of course entitled to take a different view, but they may not accuse Dr. Baccarelli of "fail[ing] to grapple with" the possibility of genetic confounding. He spent thousands of words "grappling with" essentially nothing else. Defs. ADHD Br. at 25.

Doubling down, Defendants say that Dr. Baccarelli "improperly disregard[ed] Gustavson (2021), which used a sibling analysis to control for genetic confounders." *Id.* Perhaps they did

[52] Defendants conspicuously do not suggest that "genetic confounding" is the "elephant in the room" for the *ASD* literature. That is probably because their experts admitted that "we don't have sufficient evidence to really support that as a confounding variable" for ASD. Ex. 25, Pinto-Martin Dep. Tr. at 153:15–21.

not notice the section of Dr. Baccarelli's original report entitled "sibling control design," where he discusses the results of Gustavson and other sibling-control studies at length. Ex. 1, Baccarelli Rep. at 117–22. And perhaps they overlooked Dr. Baccarelli's rebuttal report, which has another section called "sibling-controlled studies" which goes into even greater detail. Baccarelli Rebuttal Rep. at 5–7. It is unserious to claim that Dr. Baccarelli "ignored" or "disregarded" Gustavson, as the experts disregarded similar lines of evidence in *Daniels Feasal* or *Mirena*. What Defendants do not like is that Dr. Baccarelli provided ample reasons why he did not view the Gustavson paper—which was based on just 34 sets of children—as definitively washing away a body of literature involving hundreds of thousands.[53] The Gustavson study authors said the exact same thing. Ex. 80, Gustavson Supp. Information at 7 (Given the small sample size, "statistical power to detect within effects was relatively low. Hence, these results should be interpreted with caution."). So did Dr. Pinto-Martin: "Does [Gustavson] prove that this is all about genetics? No." Ex. 25, Pinto-Martin Dep. Tr. at 466:15–16. Dr. Baccarelli surely gave "legitimate reasons to question the results of" the Gustavson study, the primary study on which [Defendants] rel[y]." *In re Roundup*, 390 F. Supp. 3d at 1152.

B. Dr. Baccarelli Did Not "Cherry Pick" Outcomes.

Defendants continue their assault on the English language by claiming that Dr. Baccarelli relied on a few "isolated findings" in support of an association between APAP and ADHD. Defs. ADHD Br. at 37. The results cannot be considered isolated—Dr. Pinto-Martin admitted that "100

[53] The best criticism that Defendants can muster is that Dr. Baccarelli stated that the Gustavson analysis was based on "approximately 2-3 cases of ADHD" rather than 34. Defs. ADHD Br. at 29–30. Dr. Baccarelli regrets that error, but he accurately stated the relevant sample size for Gustavson: "only n=34 pairs contributed to the analysis." Ex. 6, Baccarelli Rebuttal Rep. at 6; Ex. 20, Baccarelli Dep. Tr. at 432:22–23 ("That's a study with only 34, perhaps, informative units."). And whether there were 2-3 cases or 34, the point remains the same: the Gustavson study is too small to make any definitive conclusions, as the authors themselves conceded. Ex. 52, Gustavson (2021) at 8 (describing the "limited statistical power" of the study and cautioning that "the results need to be replicated in other studies").

percent" of the ADHD studies on long-term APAP use that *she* chose to include in her report showed "a positive association between prenatal APAP exposure and the risk of ADHD diagnosis." Ex. 25, Pinto-Martin Dep. Tr. at 167:15–23. Thirteen of them were statistically significant. *Id.* at 170:25–171:4. It is hard to get less "isolated" than that.

Defendants also argue that Dr. Baccarelli relied "only on the positive associations" in the NDD studies while "ignoring null or negative associations." Defs. ADHD Br. at 37. That is not true—Dr. Baccarelli faithfully cataloged and analyzed all the results, whether helpful to his causation opinion or not. It is simply a fact, albeit an inconvenient one for Defendants, that almost all of the literature supports Dr. Baccerelli's conclusion.

Defendants also consistently miscategorize Dr. Baccarelli's analysis as "cherry-picking."[54] They criticize Dr. Baccarelli for saying that Liew (2014) showed a dose response because the "Liew (2014) findings relevant to dose response are inherently inconsistent." Defs. ADHD Br. at 38. That is not what Liew said. The authors stated that "higher use frequency increased risk in an exposure-response manner." Ex. 44, Liew (2014) at 319. How is it "cherry picking" a study to quote its *actual conclusions*? Defendants also tout some null results buried in the Vlenterie, Parker, and Inoue papers. Defs. ADHD Br. at 38–39. But Dr. Baccarelli never suggested that those studies strongly supported his opinion.[55] And, again, null results are to be expected even in a literature review that amply demonstrates causation. *See supra* at 40; *cf.* Ex. 35, Ref Manual at

[54] That is no surprise: The Navigation Guide methodology makes it impossible to "cherry pick." All the studies must be included and then evaluated based on criteria identified in advance. When using that kind of method, it is simply not possible to rely only on favorable outcomes. All the outcomes must be (and were) included in the analysis.

[55] That said, the study authors did report some supportive findings. For example, the Vlenterie study stated that "[l]ong-term exposure to paracetamol in utero was associated with modestly increased risks of motor milestone delay and impaired communication skills" and that "[c]aution is warranted when considering long-term use of paracetamol." Ex. 108, Vlenterie (2016) at 1998. The Parker study stated that "acetaminophen use during pregnancy was weakly associated with mother-reported behaviour problems." Ex. 175, Parker (2019) at 307. And the Inoue study stated that "Our study corroborates published associations between prenatal exposures to acetaminophen and behavioral problems and extends the literature to early adolescence." Ex. 176, Inoue (2020) at 1009.

606 ("[N]ot infrequently, the scientific record may include a number of epidemiologic studies whose findings differ.").

Finally, Defendants accuse Dr. Baccarelli of cherry-picking because he did not account for "multiplicity bias," an esoteric species of chance finding. Defs. ADHD Br. at 39; *id.* at 2 (speculating that the findings might be "due to the play of chance alone" given "the risk of multiplicity errors"). This criticism is truly made for litigation. Not a single study author suggested that *all* of the results in this literature could be the result of chance. Dr. Pinto-Martin would not go where Defendants' lawyers have ventured. Ex. 25, Pinto-Martin Dep. Tr. at 172:12–18 ("Q. You're not suggesting that you can get 13 statistically significant results in a row due to chance are you? A. I don't believe I said that anywhere in my report."). Dr. Baccarelli was hardly "cherry picking" by not endorsing a theory that only defense lawyers think is possible.

III. Dr. Baccarelli's Bradford Hill Analysis Was Reliable for Both ASD and ADHD.

In their two primary briefs, Defendants argue that Dr. Baccarelli "did not conduct [a] reliable Bradford Hill analys[is]" for *any* of the *nine* Bradford Hill factors. Defs. ASD Br. at 47, 62; Defs. ADHD Br. at 41. In Defendants' telling, Dr. Baccarelli—the chair of epidemiology at Columbia University—somehow could not even manage to reliably evaluate *one* of the *nine* Bradford Hill factors, the seminal method for making causal inferences in his field. *Cf. Fifth Third Mortg. Co. v. Chicago Title Ins. Co.*, 692 F.3d 507, 509 (6th Cir. 2012) ("When a party comes to us with nine grounds for reversing the district court, that usually means there are none.").

In support of this brazen argument, Defendants misrepresent what the study authors themselves concluded about their own data, what Bradford Hill himself said about his own methodology, or both. Although Defendants may disagree with Dr. Baccarelli's conclusions, "scientists reliably applying the Bradford Hill factors may reasonably come to different conclusions about whether a causal inference may be drawn." *Abilify*, 299 F. Supp. 3d at 1307

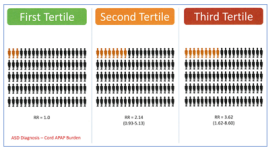
(citing *Milward*, 639 F.3d at 18). And Defendants do not identify any flaws in Dr. Baccarelli's application of the Bradford Hill factors—certainly not a "flaw that is large enough that the expert lacks good grounds for his conclusions." *Amorgianos*, 303 F.3d at 267 (cleaned up).

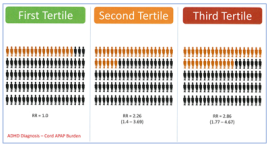
A. Dr. Baccarelli Was Right to Conduct a Bradford Hill Analysis for Both ASD and ADHD.

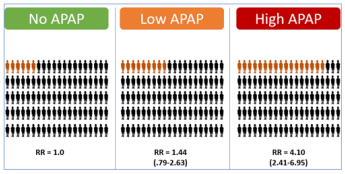
Defendants first argue that a Bradford Hill analysis was not even proper here because the association between prenatal APAP exposure and ASD is not "perfectly clear cut." Defs. ASD Br. at 47–48. That is wrong for the reasons stated above. *See supra* at 34–43. For precisely that reason, the Alemany study authors conducted a Bradford Hill analysis for ASD. *See* Ex. 37, Alemany (2021) at 1000; Ex. 25, Pinto-Martin Dep. Tr. at 246:6–9 (conceding that the Alemany authors are "doing a Bradford Hill analysis").

B. Dr. Baccarelli Reliably Analyzed the Strength Factor.

Dr. Baccarelli accurately characterized the strength for the various studies. He candidly admitted that "in many of the studies, the magnitude of the association was moderate, with risk ratios between 1.0 and 2.0." Ex. 1, Baccarelli Rep. at 159. As he also pointed out, however, many of the results were much higher. The Ji and Baker studies showed risk ratios of above 2.0 and indeed 3.0. *Id.* at 160. Those are undeniably strong associations, as is evident even visually.







Ex. 40, Pinto-Martin Dep. Ex. 637; Ex. 41, Pinto-Martin Dep. Ex. 638. They are an order of magnitude stronger than the (causal) association for secondhand smoke and lung cancer. These

high risk ratios provide further evidence against confounding as well: "The higher the relative risk . . . the lower the chance that the effect is spurious." Ex. 35, Ref Manual at 602.

Meanwhile, modern epidemiologists consider not only "magnitude" but also "statistical significance" as "the accepted benchmark for judging the strength of an observed association, and thus its potential causality." Ex. 1, Baccarelli Rep. at 160 (quoting Fedak (2015)). And as detailed above, there are more than a dozen statistically significant results in this literature.[56] In light of those results, and given Bradford Hill's own admonition that there are no hard-and-fast numerical cutoffs when evaluating strength,[57] Defendants have no basis to say that Dr. Baccarelli was unreliably applying his methodology.

Defendants claim that "strength" is a "gating factor" for any Bradford Hill analysis to proceed. Defs. ASD Br. at 49; Defs. ADHD Br. at 41. To the extent that they are suggesting that only associations above 2.0 can be causal, they are mistaken. "[T]here's not a right number that you need to exceed" for an association to be deemed strong. Ex. 25, Pinto-Martin Dep. Tr. at 47:17–19; *see also* Ex. 63, Modern Epidemiology at 64 ("There is no general rule for how large an association needs to be to meet this consideration."). The risk ratios for secondhand smoke are less than 2.0. The same is true for the associations between valproic acid and ADHD, between air pollution and mortality, and between smoking and heart disease. These associations are considered causal.

Whatever is meant by "strength" being a "gating factor," there is no reason to think this literature does not pass through the gate. Although there have been some "fallacious" attempts to

[56] Defendants criticize Dr. Baccarelli for "erroneously conflat[ing] strength of association with consistency, which are analytically distinct." Defs. ASD Br. at 51; Defs. ADHD Br. at 43-44. But Dr. Baccarelli specifically stated that the number of statistical associations "also relates to consistency, which I discuss below." Ex. 1, Baccarelli Rep. at 159. He did not conflate the two factors; he explained how they were related.

[57] "[T]here are many occasions in medicine" when the risk ratios are small. Ex. 69, Bradford Hill at 296.

"set sharp boundaries to identify causal associations, such as at a doubling of the risk," Ex. 63, Modern Epidemiology at 64–65, the literature here would pass through even that (fallacious) needle-eye. The studies that measured APAP levels directly via cord blood and meconium produced risks that were doublings and triplings.[58] As independent authors working on this topic have noted, those are "large" "effect sizes." Ex. 70, Bauer (2021) Consensus Statement at 763.[59]

C. Dr. Baccarelli Reliably Analyzed the Consistency Factor.

Defendants next argue that Dr. Baccarelli failed to reliably apply the consistency factor, which simply asks whether an association has been "repeatedly observed by different persons, in different places, circumstances, and times." Ex. 69, Bradford Hill at 296. The answer is obviously "yes." The studies have examined cohorts of hundreds of thousands of women and children from around the world, have been conducted by separate teams of researchers, and have used widely varying study designs. Numerous study authors have said explicitly that the results are consistent. *See, e.g.*, Ex. 43, Bauer & Kriebel (2018) at 134 ("First, there is the consistency; all nine studies suggest a moderate increase in risk."); Ex. 42, Olsen & Liew (2017) at 1395 ("[F]ive different prospective cohorts have consistently estimated a positive link."); Ex. 54, Gou (2019) (similar). The Alemany authors explicitly found that the consistency criterion *of Bradford Hill* was satisfied. Ex. 37, Alemany (2021) at 1000 ("Consistency is supported because we observed consistent results using a variety of populations and methods.") Defendants are again inviting the Court to exclude Dr. Baccarelli for saying what the peer-reviewed literature says.

[58] Defendants are of course correct that "Hill originally identified as supportive of causation" examples of nine or ten -fold increase in risk. Defs. ASD Br. at 49. But one must remember that Bradford Hill was assessing the link between tobacco and lung cancer—a uniquely powerful literature. There are few (if any) other causal risk factors that show that kind of strength. That hardly means they are not causal.

[59] Defendants are correct—as a general matter—that the higher the relative risk, the lower the likelihood of a confounder or bias being able to explain the entire effect. Defs. ASD Br. at 51. But as independent scientists have noted, the results here are so "large" in the studies that directly measured APAP levels that "residual confounding by uncontrolled factors is a less likely explanation for [the] identified associations." Ex. 70, Bauer (2021) Consensus Statement at 763.

Defendants' first response is a false non sequitur. They say that Dr. Baccarelli's view on the consistency of the ADHD literature is "contrary to the FDA." Defs. ADHD Br. at 44. But the FDA states, in the conclusion of its 2022 review, that the "studies examined in this review along with the reviewed meta-analyses suggest a consistent association between APAP or long durations of prenatal APAP exposure and ADHD." Dkt. 483-1 at FDACDER000114.

Next, Defendants criticize Dr. Baccarelli for opining that "a set of results is consistent even if some of the results are not statistically significant." Defs. ASD Br. at 53–54. But the Rothman *Modern Epidemiology* textbook, considered the authoritative text in the field, says: "It is sometimes claimed that a literature or set of results is inconsistent simply because some results are 'statistically significant' and some are not. This sort of evaluation is completely fallacious." Ex. 63, Modern Epidemiology at 66. Defendants will be hard pressed to find a Rule 702 case requiring exclusion because an expert *refused* to engage in "completely fallacious" evaluations.

Finally, Defendants suggest that a body of literature cannot be consistent if there are *any* studies with "point estimates below 1.0." Defs. ASD Br. at 54. But consistency has never meant *uniformity*. The second-hand smoke literature has many non-significant results and multiple point estimates below 1.0. *E.g.*, Ex. 67, Surgeon General Report at 436. The vast majority of the studies here show a positive, statistically significant association.

D. Dr. Baccarelli Reliably Evaluated the Specificity Factor.

Defendants are so reflexive in their criticisms of Dr. Baccarelli they cannot take "yes" for an answer. Dr. Baccarelli found that specificity is *not* satisfied—the answer they agree with. Ex. 1, Baccarelli Rep. at 162. Defendants nonetheless complain that he did not give this finding enough weight. But Bradford Hill himself cautioned not to "over-emphasize the importance of the characteristic" because many causal agents do not exhibit specificity. Ex. 69, Bradford Hill at 297; *see also* Ex. 63, Modern Epidemiology at 67 ("The limitations of this form of specificity are

apparent even in the case of smoking and lung cancer.").[60] When specificity is satisfied, it is extraordinarily compelling evidence of causation; when it is not, it tells us very little. That is what Bradford Hill said. So did Dr. Baccarelli.

E. Dr. Baccarelli Reliably Evaluated the Dose Response Factor.

Defendants accuse Dr. Baccarelli of "misrepresent[ing] the scientific literature on the fundamental question of dose response," Defs. ADHD Br. at 46, but Defendants' accusation flies in the face of that literature. The Bauer and Kriebel review, for example, says that "there was evidence of a dose-response gradient." Ex. 43, Bauer & Kriebel (2018) at 134. Baker says "a dose-response association was detected." Ex. 71, Baker (2020) at 1073. Liew (2014) says "higher use frequency increase[ed] risk in an exposure-response manner." Ex. 44, Liew (2014) at 319. Liew (2016a) says "dose-response patterns were observed." Ex. 45, Liew (2016a) at 953. Ji said that "there were dose-response patterns." Ex. 46, Ji (2020) at 186. Ricci said that their meta-analysis "suggest[ed] a dose-response effect." Ex. 33, Ricci (2023) at 11. The Alemany meta-analysis said that the dose-response factor of Bradford Hill was satisfied. Ex. 37, Alemany (2021) at 1000. Whatever else might be said about this literature, Dr. Baccarelli was surely entitled to espouse the same view of dose response that more than a half-dozen of the studies have espoused.[61]

F. Dr. Baccarelli Reliably Evaluated Biological Plausibility.

Continuing their practice of redefining words to suit their position, Defendants argue that biological *plausibility* is not satisfied because the precise injury mechanism is not known with

[60] There are some examples of true specificity, called "signature diseases" in which the disease does "not occur without exposure to an agent." Ex. 35, Ref Manual at 570. Examples include asbestos and asbestosis and DES exposure and vaginal adenocarcinoma. *Id.* at 609. But those examples are the rare exception rather than the rule.

[61] Defendants concede that "dose response is considered by some to be the 'single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect.'" Defs. ASD Br. at 56. That so many independent study authors have deemed it satisfied is not only powerful evidence that Dr. Baccarelli's causation opinion is reasonable—though of course it is that. It is powerful evidence that his opinion is in fact correct. *See* Ex. 35, Ref Manual at 603 ("A dose-response relationship is strong, but not essential, evidence that the relationship between an agent and disease is causal.").

certainty. Defs. ASD Br. at 58; Defs. ADHD Br. at 49–50; Defs. Mechanism Br. at 14, Dkt. 1165. That is obviously the wrong standard. *See Fosamax*, 645 F. Supp. 2d at 183 ("That the mechanism remains unknown does not mean that the one proposed by [plaintiff's] experts is not widely accepted as plausible."). As Dr. Pinto-Martin stated, plausible does not mean certain; it means "possible." Ex. 25, Pinto-Martin Dep. Tr. at 542:22–25. That is correct: biological plausibility asks "if it appears reasonable or realistic within the context in which the hypothesized cause and effect occur." Ex. 63, Modern Epidemiology at 69. Dr. Baccarelli identified multiple "reasonable or realistic," "possible" mechanisms by which prenatal APAP exposure can cause ASD and ADHD. Ex. 1, Baccarelli Rep. at 44–51, 164. The Alemany authors identified many of the exact same mechanisms before ultimately concluding that the biological plausibility factor was satisfied. Ex. 37, Alemany (2021) at 1000. Defendants offer no reason why Dr. Baccarelli's opinion on this factor is unreliable.

G. Dr. Baccarelli Reliably Evaluated Coherence.

Coherence simply means that causation should not "seriously conflict" with "generally known facts" about a disease. Defs. ASD Br. at 59. Defendants identify no serious conflicts. Dr. Baccarelli noted that causation is consistent with "environmental factors" in pregnancy being known to affect neurodevelopment, that causation from APAP is certainly consistent with the rise in rates of NDDs seen over the past decades, that causation is consistent with studies showing a link between a country's ASD rates and its use of APAP, and data suggesting that the rates of ASD and APAP use appear to have moved in tandem. Ex. 1, Baccarelli Rep. at 165. Defendants suggest that other forces are at work, in particular their rather offensive hypothesis that families are simply obtaining ASD diagnoses in order to obtain "access to educational services." Defs. ASD Br. at 60. They are welcome to offer that wild conjecture to juries next year. But they never identify any "generally known" feature of ASD or ADHD that would "seriously conflict" with a causal

link. Ex. 69, Bradford Hill at 296. That is why, like Dr. Baccarelli, the Alemany authors stated that the "coherence" factor was satisfied. Ex. 37, Alemany (2021) at 1000.

H. Dr. Baccarelli Reliably Evaluated Temporality.

Defendants do not even agree that Dr. Baccarelli reliably evaluated the temporality criterion. The question is simply about the potential for reverse causation: "which is the cart and which the horse?" Ex. 69, Bradford Hill at 297. Here that means excluding the possibility that the child's ASD or ADHD diagnosis might have caused the mother to take APAP while pregnant. That was not a difficult possibility to exclude. Most of the studies employed prospective cohort designs, in which women were asked *at the time of pregnancy* whether they took APAP. Then, *years later*, the cohort studies looked at whether their children were diagnosed with ASD or ADHD. These kinds of studies "can conclusively establish the temporal relationship between exposure to a chemical and a disease." *In re Roundup*, 390 F. Supp. 3d at 1123.[62] In the absence of a "time machine," even Defense expert Dr. Pinto Martin had to admit that reverse causation was impossible. Ex. 25, Pinto-Martin Dep. Tr. at 537:5–538:9.[63] Defendants' criticism on this point is so bizarre that it should cause the Court to question their credibility more broadly.

I. Dr. Baccarelli Reliably Evaluated Analogy and Experiment.

Dr. Baccarelli did not place much weight on the analogy and experiment factors, admitting that they can produce erroneous results when weighed too heavily. Ex. 1, Baccarelli Rep. at 169–70. Defendants still say he got them wrong. Defs. ASD Br. at 61; Defs. ADHD Br. at 53. Their

[62] *See also* Ex. 35, Ref Manual at 558 ("One advantage of the cohort study design is that the temporal relationship between exposure and disease can often be established more readily.").

[63] Defendants suggest that Dr. Baccarelli testified that "acetaminophen has the same purportedly causative impact on ASD nine months into a pregnancy as it does on the day an egg is fertilized." Defs. ASD Br. at 59. The Court will find no such testimony in Dr. Baccarelli's deposition—certainly not on the pages that Defendants identify. *Id.* at 59 (citing Ex. 20, Baccarelli Dep. Tr. 91:18–92:12, 92:23–93:24)). In reality, he simply testified that the human epidemiological data was not fine-grained enough to identify the "most susceptible" window of pregnancy. Ex. 20, Baccarelli Dep. Tr. 93:12–24.

throwaway argument spans just a paragraph as to *both* factors. And it is mistaken. The analogy criterion asks whether drugs with similar mechanisms have shown similar effects, Ex. 69, Bradford Hill at 299; Ex. 63, Modern Epidemiology at 71, and as Dr. Baccarelli points out, valproic acid and APAP have similar effects on the developing fetus—increasing oxidative stress and depleting glutathione levels—and the valproic acid label states that it most likely causes ASD and ADHD. Ex. 1, Baccarelli Rep. at 167–68. The analogy holds.

The experiment factor, meanwhile, asks whether the "frequency of the associated events [is] affected" when "some preventive action is taken." Ex. 69, Bradford Hill at 298. Dr. Baccarelli carefully explained that "we do not have traditional experimental evidence," Ex. 1, Baccarelli Rep. at 169—because Defendants have not yet taken any "preventive action" with respect to APAP that would allow researchers to determine whether ASD and ADHD rates dropped in response. But he (correctly) noted that there was still experimental data in the form of animal studies, lab studies, ecological studies, and human pharmacokinetic studies. Those are entirely valid forms of evidence to consider. Ex. 63, Modern Epidemiology at 71 ("Experimental evidence can refer to clinical trials, to animal experiments, or to experiments on tissues.").[64]

IV. Dr. Baccarelli Reliably Applied the Navigation Guide Methodology.

Dr. Baccarelli reliably applied the Navigation Guide methodology as a tool to systematically evaluate the scientific literature such that it can be replicated and tested. *See Daniels-Feasel*, 2021 WL 4037820, at *21. "The Navigation Guide methodology is a systematic and rigorous approach to research synthesis that has been developed to reduce bias and maximize transparency in the evaluation of environmental health information." Ex. 34, Woodruff & Sutton

[64] Defendants criticize the use of ecological data. To be sure ecological data is not as probative as analytic epidemiology—in particular, the large, prospective cohort studies that provide the bulk of the evidence here. But ecological data certainly still has a role to play. The link between thalidomide and birth defects was first detected via ecological studies. Ex. 35, Ref Manual at 562.

(2014) at 1007. The "overall architecture [of the Navigation Guide] is based on empirically proven and/or time-tested methods," mostly the Grading of Recommendations Assessment, Development and Evaluation, known as GRADE. *Id*. at 1012.[65]

As Defendants recognize, the Navigation Guide methodology involves four steps: (1) specification of the study question, (2) selection of evidence, (3) rating the quality and strength of the evidence, and (4) grading the strength of the recommendation. *Id.* at 1008. Dr. Baccarelli properly applied all four steps. *See* Ex. 1, Baccarelli Rep. at 3, 12–23, 138–58. He set forth objective grading standards *a priori* and applied them to collected studies, which were gathered using defined search criteria, all resulting in a fully transparent summary of his evidence, analysis, and grading. *See id*.

Defendants claim that the Navigation Guide is "aimed not at proving causation" and "employs a lower standard than a scientific causation approach." *None* of the cases cited by Defendants support those contentions. They instead address FDA's standard of review for determining the safety of drugs. *See In re Zicam Cold Remedy Mktg., Sales Pracs., & Prods. Liab. Litig*., No. 09-2096, 2011 WL 798898, at *11 (D. Ariz. Feb. 24, 2011); *In re Mirena Ius Levonorgestral-Related Prods. Liab. Litig. (No. II)*, 387 F. Supp.3d 323, 356 (S.D.N.Y. 2019) ("[W]hen evaluating pharmaceutical drugs, the FDA often uses a different standard than a court does to evaluate evidence of causation in a products liability action."). How these cases pertain to Dr. Baccarelli's use of the Navigation Guide is a mystery. *Ipse dixit* notwithstanding, the

[65] The Navigation Guide methodology was developed in part to provide appropriate weight and consideration to observational studies, which "are recognized a being a reliable source of evidence in the clinical sciences because not all health care decisions are, or can be, based on RCTs (randomized controlled clinical trials)." *Id*. at 1011; *see also* Ex. 6, Baccarelli Rebuttal Rep. at 17 ("Navigation Guide differs from GRADE in that it was created to address the differences in the types of evidence available to assess environmental hazards [] that…do not have [RCTs], as is usually the case with clinical science.").

Navigation Guide is routinely employed to evaluate causation. Ex. 72, Mari-Bauset (2018) at 4–5 (whether pregnancy exposure to endocrine disrupting chemicals is associated with increased risk of ASD); Ex. 73, Lam (2017) at 086001-2 (whether exposure to polybrominated diphenyl ethers affects either intelligence or attention); Ex. 74, Johnson (2016) at 717–18 (whether exposure to triclosan has adverse effects on human development or reproduction). Dr. Baccarelli likewise has used the Navigation Guide in his work outside litigation to determine causation. Ex. 20, Baccarelli Dep. Tr. at 309:2–14; *see also id*. at 304:9–305:8.

Defendants claim Dr. Baccarelli did not apply the Navigation Guide "in a methodological manner," "did not perform [the Navigation Guide] steps reliably," and "his entire review of the evidence was results-oriented," but Defendants fail to cite a single example to support these wholly conclusory contentions.[66] Defendants' last-ditch Navigation Guide argument is that Dr. Baccarelli's individual evaluation was improper because of the "obvious potential for bias in this circumstance." That potential is apparently so "obvious" Defendants do not bother to explain it. The Navigation Guide's first step of a "predefined protocol," which Dr. Baccarelli implemented, actually "reduces the impact of review author[] biases." Ex. 34, Woodruff & Sutton (2014) at 1009. Defendants' may not like the results of Dr. Baccarelli's application of the Navigation Guide methodology, but that is no ground to exclude his testimony.

CONCLUSION

Defendants' Motions to Exclude Dr. Baccarelli should be denied.

[66] Defendants briefly criticize Dr. Baccarelli for giving "weak" scores to studies showing less evidence of an association and "moderate" or stronger scores to studies showing a strong association. Defs. ADHD Br. at 13; Defs. ASD Br. at 17 (similar). But as Defendants implicitly concede, he did not simply mark "strong" for studies showing an association—some of them were graded "moderate." And in any event, this is what one would expect for a literature analyzing a *real* association—better designed studies will show it more clearly; worse-designed studies might miss it.

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Respectfully submitted,

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